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Public Health

The order in this section is:—**General; Vital Statistics; Epidemiology; Maternal and Child Health; Health of Students, Nurses and Hospital Staffs; Health of Old Persons and the Chronically Ill; Chronic Cardio-Respiratory Diseases; Chronic Rheumatism; Cancer; Miscellaneous Diseases; Dental Health; Mental Health.**

GENERAL

MINISTRY OF HEALTH. **Report of the Ministry of Health for the Year ended 31st December, 1960. Part I. The Health and Welfare Services.** Cmnd. 1418. pp. xvii + 269. [Refs. in footnotes.] 1961. London: H.M. Stationery Office. [12s.]

The form of this annual report has been slightly changed from the previous year [see this *Bulletin*, 1960, v. 35, 1153]. There is an introductory chapter and the presentation statement by the Minister, the Rt. Hon. J. Enoch POWELL, occupies only 5 lines compared with the 3½ pages of that of his predecessor. There are new chapters on the development of the psychiatric services and on the report of the Royal Commission on the remuneration of doctors and dentists: there is no longer a separate section on the welfare services, a description of which is included in the chapter on the local authority services. There are, also, new chapters on the Executive Councils, Food Safety and Hygiene and on Civil Defence.

Finance. The total gross cost of the National Health Service in 1959–60 was £726m., an increase of 8·2% on the previous year. The hospital and specialist service took £415m. compared with £383m. and other substantial increases were pharmaceutical from £69m. to £76m., general dental from £46m. to £50m. and local authority services from £59m. to £68m.

Mental Health. Present trends are based on the following points: (1) mental hospitals should be places for treatment rather than for custody; (2) local authorities should provide community services such as hostels, training and social centres and visiting services; (3) there should be psychiatric wards in general hospitals. A result of these trends should be that in the future there will be fewer long-stay patients and the hope is expressed that in the next 16 years the beds needed in mental hospitals may fall from the present 152,000 to about 80,000. The reasons for this hope are set out and discussed. Different considerations apply to the mentally sub-normal as distinct from the mentally ill and the prospect of a reduced demand for beds is by no means so rosy. Local authorities are taking their new duties seriously and are cooperating well with the hospital authorities. During the year 53 new training centres were opened. The need in all branches of the psychiatric services for more and better trained staff is well brought out.

Hospital and specialist services. The number of available staffed beds at the end of 1960 was 473,000, 2,000 fewer than in 1959. The occupied beds at the end of the year were 410,000 compared with 413,000 a year earlier, and the number of "discharges and deaths" increased from 4,080,000 to 4,221,000.

Capital expenditure on hospitals was £20,500,000 and is to be increased to £31m. in 1961–62. The Ministry are producing "building notes" on hospitals and have organized an exhibition of hospital plans. The Ministry are developing their work study section and have started an abstracting service on hospital administration.

The number of consultants is now 7,292 compared with 7,102 a year earlier. The more junior grades of whole-time hospital medical staff contain 8,272 doctors of whom no fewer than 3,408 were born outside Great Britain. Whole-time nursing staff numbered 151,721 and part-time 42,715.

Greater use is being made by the hospitals of the opportunities to obtain supplies through government channels and so take advantage of bulk buying.

The general medical service. The number of principals providing unrestricted medical services increased during the year by 182 to 19,905: 70·3% were in partnership and the average number of patients on each doctor's list was 2,287. The proportion of the population living in areas where more doctors are needed increased from 19·9 to 20·1%. There are 15,849 practitioners on the obstetric lists.

The pharmaceutical service. The number of prescriptions and the average cost per prescription continue to go up: the former being 218,685,118 compared with 214,029,087 and the latter 86·92d. (81·76d.). A clinical trials committee has been set up to give advice about the trial of new drugs.

The general dental service. Courses of treatment increased from 10,700,459 to 11,539,290 and the number of dentists in the service rose from 10,145 to 10,254. The number of first-year dental students decreased from 622 to 609.

The new chapter on *Executive Councils* deals mainly

with disciplinary action. Considering the size of the service the number of cases is remarkably small. The total referred by the Councils to the Minister was 1,268 of which 441 related to the pharmaceutical service and only 410 to the general medical, and in 75% of the latter no breach of the regulations was found.

Local authority services. Vaccination against poliomyelitis by local authority staff is now available to everyone under the age of 40 years as well as to expectant mothers and certain specified groups subject to special risk. Patients over 40 can be vaccinated by their own doctors who can obtain the vaccine on a National Health prescription form. The great bulk of the vaccine used in 1960 was of British manufacture though a little was imported from Canada for patients sensitive to penicillin.

As a result of publicity and a few sharp local outbreaks of diphtheria the "diphtheria immunity index for children under five" is now 60·7%.

A further 83 authorities, making 108 in all, now have an approved chiropody service. 56 new purpose-built clinics for maternal and child welfare have been opened. The number of first attendances at ante-natal clinics increased by 2·8% to 261,000 and the total attendances at child welfare centres by 1% to 10,302,000.

Domiciliary confinements attended by midwive numbered 275,921 and were 37% of all confinements.

There were 7,203 health visitors in office compare with 7,033 in the previous year: they paid 12,207,00 visits. District nurses numbered 10,322 and pai 23,083,425 visits, a slight reduction on the previous year but the number of households attended by the domesti help service rose from 289,500 to 312,013.

There are enlightening observations on the welfare o the elderly and the handicapped, and emphasis is lai on the need for close cooperation between voluntary an statutory bodies. There are now the names of 93,36 handicapped on the official lists.

Professional matters. Courses of instruction for socia workers are being established and a school for denta auxiliaries has been opened. The steps being taken fo the registration of professions supplementary to medicin are described.

Other. The 104 pages devoted to tables are full o detailed information.

The report is again essential reading for all concerne in the administration of the National Health Service an the best source of information for those from abroad wh are studying health problems on a national scale.

Allen Daley

MATERNAL AND CHILD HEALTH

MOLLER, M. S. G. **Custom, Pregnancy and Child Rearing in Tanganyika.** *J. Trop. Pediatrics.* 1961, Sept., v. 7, No. 2, 66–80.

GREENBERG, M. & VANDOW, J. E. **Ophthalmia Neonatorum: Evaluation of Different Methods of Prophylaxis in New York City.** *Amer. J. Pub. Health.* 1961, June, v. 51, No. 6, 836–45. [28 refs.]

This disease has virtually disappeared in the more advanced communities but is still of importance where the incidence of gonorrhoea is high and living standards low. The Credé method of instillation of silver nitrate was first used in Leipzig in 1881 and has been in vogue ever since. In New York City the disease rate fell from a high point of 37·49 per 100,000 live births in 1944 to 1·81 in 1956 (no case was reported in 1951 and 1953).

In order to ascertain the prevalence of this condition data were collected from 96 hospitals (57 voluntary which accepted private and ward patients, 15 municipal with ward patients only, and 24 proprietary hospitals wit private patients only). In 472,580 births 49 cases c gonococcal ophthalmia neonatorum were found; a regards type of prophylaxis 22 cases occurred wher there was none, 1 where saline only was used, 17 afte silver nitrate instillation, 9 after local antibiotic applica tion and none after intramuscular penicillin injection; 2 cases occurred in voluntary, 28 in municipal and none i proprietary hospitals, the rates being 7·2, 27·4 and 0 pe 1,000 respectively.

An analysis of the figures which are set out in 4 table shows that not only methods of prophylaxis but ho and environmental factors affected the results. Penicilli injection gave far the best results; none of the othe methods proved very effective though silver nitrate wa better than no prophylaxis. Local conditions, standar of living and incidence of gonorrhoea, are the mo important factors and the desirability of prophylax should depend on these; where risk of infection is ver low prophylaxis is unnecessary. *T. E. Osmond*

CHRONIC CARDIO-RESPIRATORY DISEASES

PELL, S. & D'ALONZO, C. A. **A Three-Year Study of Myocardial Infarction in a Large Employed Population.** *J. Amer. Med. Ass.* 1961, Feb. 11, v. 175, No. 6, 463–70, 3 figs. [17 refs.]

This is a careful study of the frequency of myocardial infarction in different age and sex groups within occupations ranging from labourers to senior executives, in a large chemical firm with employees residing mainly i the Middle-Atlantic and South-Eastern States. Ever employee is medically examined annually above the ag of 30 and biannually below it. A special insurance fun covering benefits for death or disability lasting more tha 7 days provided information on the incidence and fatalit rate of coronary thrombosis or myocardial infarction c both. Among 89,089 employees of both sexes there wer

653 incidents of this kind during the 3 years 1956–58. Analysis of the data showed the usual male preponderance particularly in the younger age-groups. Less conventional, however, is the finding that the incidence rate is highest in the lower middle paid salaried staff and lowest in the highest paid men. The pay roll workers had an intermediate level of morbidity, perhaps because of the physical activity involved in their jobs. Attacks seldom occurred during violent exertion but were most frequent during rest or sleep. They were equally likely to occur at home, at work or on holiday. The case fatality rate within 30 days of the attack averaged 31·4% and was related to the patient's age and pre-existing hypertension in men over 50. Neither obesity nor exertion at the time of attack appeared to be relevant; attacks at work were less serious than those occurring during sleep.

A comparison of the previous history of medical examinations and illnesses in these 653 patients with controls matched by age, sex, pay group and geographical location showed that infarction is commoner in men with hypertension, peptic ulcer, gall bladder disease, diabetes and, in those under 45, over-weight. The blood group was of no special significance. Three-quarters of the patients had apparently normal electrocardiograms before the attack but T wave changes, S-T-T abnormalities, premature auricular and ventricular contractions and bundle branch block were more frequently found in their tracings than in those of the matched controls.

[This is an excellent example of the value of the careful analysis of data drawn from routine medical examinations and sickness records in industry.]

D. D. Reid

FLETCHER, C. M. & TINKER, C. M. **Chronic Bronchitis. A Further Study of Simple Diagnostic Methods in a Working Population.** *Brit. Med. J.* 1961, May 27, 1491–8, 4 figs. [17 refs.]

A survey of respiratory symptoms, sputum volumes and ventilatory capacity is described which was carried out at the London Transport Executive Works at Chiswick and Acton. All men aged 30–59 received a short questionary with their payslips which they were asked to complete and return: a one in five random sample was then made and these men invited to attend for interview. After completion of a further questionary the ventilatory capacity was estimated by means of the Wright peak flow meter and bottles were issued to the men for early morning sputum specimens.

Of those interviewed 363 men aged 40–59 were selected for study and the results are presented in a series of tables and figures. There were 2 observers, and although the mean age of the men interviewed by each was almost identical, differences in their findings were noted in a number of respects but it is concluded that sampling differences accounted for the discrepancies.

The figures obtained in this investigation were compared with those found by FLETCHER *et al.* [this *Bulletin*, 1960, v. 35, 17] in London postmen, and except for cough on rising, which was more prevalent at the GPO, most of the other findings in the two groups were similar. However, the number of postmen who admitted to "weather affecting the chest and causing dyspnoea" was nearly twice as great as in the LTE workers and there is an even greater contrast in the prevalence of chest illnesses causing loss of time from work. Workshop staff at LTE have fewer periods of sickness absence certified as due to bronchitis than postmen and the average duration of spells of absence is greater. This suggests that the LTE men do not stay off work so readily for minor chest illnesses as the postmen. Nevertheless, comparison with results of other population surveys showed that the incidence of chest illness in London postmen is similar to that recorded in men living in other cities and towns in the United Kingdom, while that of the LTE men is much lower. This low prevalence seems to extend also to other employees of the LTE and although various explanations are canvassed to account for this finding it is concluded that only prospective studies could establish the true incidence of recurrent bronchitis in these populations; they are also needed to reveal the reason for the association of large volumes of sputum with a greater incidence of chest illnesses and lower ventilatory capacity. This survey was in fact designed to provide a basis for just such a study.

Chest illnesses and chest colds were more frequent in men with greater sputum volumes but there was no difference between those with no sputum and those with less than 2 ml. of sputum. This relationship was similar to that found at the GPO. Only 3 sputum specimens were purulent and no relationship was found between volume of sputum and purulence. Subjects with mucopurulent sputum had no more frequent chest illnesses or chest colds and the peak expiratory flow rates were not reduced compared with those whose sputum was mucoid. The relationship between present smoking habits, cough, phlegm production and chest illnesses was similar in the 2 surveys.

Smokers in nearly all respects were worse off than the non-smokers and the ex-smokers, and various explanations to account for this finding are discussed. The measurements of peak expiratory flow for both the LTE and GPO surveys have been standardized to age 40 to facilitate comparison but none of the differences between the two groups was significant and, in both, the mean expiratory flow rate declines with increasing sputum volume, with the one exception that postmen with no sputum had slightly lower figures than those with less than 2 ml. of sputum. This may be due to a failure by some postmen to cooperate in sputum tests and they have thus been falsely included in the no-sputum group. On the other hand a large proportion of men who produced sputum had normal peak flow rates. At LTE the smokers had lower values than non-smokers or ex-smokers and a low figure noted among non-smokers at GPO is attributed to observer variation in the use of the peak flow meter. Although the Wright peak flow meter is a rapid and simple method of estimating ventilatory capacity it is less discriminating than measurements of forced expiratory volume as well as being liable to observer variation. Fletcher *et al.* [*loc. cit.*] suggested that simple bronchitis could be graded either in accordance with answers to questions on phlegm production or on the volume of morning sputum in the winter, and a close relationship in this respect was noted which

was almost identical in both surveys; confidence is thus increased in the usefulness of these techniques both in clinical and epidemiological studies.

Comparison of the answers in the written and verbal questionaries showed a close correspondence but there was a lapse rate of 10% on the written questionary and the questions about phlegm production were not answered by a further 30% of the men. The lapse rate in the GPO workers was only 7% and it is concluded that a written questionary should be more reliable in a population used to clerical work. Despite the high lapse rate the questionary which the men filled in themselves is held to be a useful screening procedure and might also enable studies to be made of death rates from bronchitis and lung cancer in relation to symptoms as well as smoking habits in large populations.

[There were considerable differences in the findings of the two observers despite much care to standardize technique. Although the discrepancies are attributed by the authors chiefly to sampling differences they do not seem to be quite certain (in their minds at any rate) as far as the recording of chest illnesses causing absence from sickness over a period of 3 years is concerned, since in the text of the paper they express doubts about the possible effects of variations due to both observers and subjects in this respect.] *G. F. Keatinge*

CANCER

CAMPBELL, A. H. **The Relationship between Cancer and Tuberculosis Mortality Rates.** *Brit. J. Cancer.* 1961, Mar., v. 15, No. 1, 10–18, 4 figs. & 1 diagram. [15 refs.]

It has previously been reported that in England and Wales the sum of the crude death rates from tuberculosis and neoplasms has remained constant over a long period of years [this *Bulletin*, 1957, v. 32, 959]. This is now shown to be true also for Australia. It is, however, found that in different areas and in different social groups the tuberculosis and cancer rates are positively correlated with one another so that a high death rate from cancer is accompanied by a high death rate for tuberculosis.

These findings cannot both be explained by any hypothesis of a direct causal relationship between cancer and tuberculosis (or healed tuberculosis). Moreover, if age standardized rates are studied the constancy of the sum of the rates disappears. The facts can be explained simply on the grounds that improved social welfare and health services contribute to the decrease of tuberculosis and at the same time lead to ageing of the population. This in turn leads to an increase of the crude cancer rate. The correlation betwen the rates in different populations can be attributed to a similar effect on both rates of urbanization and industrial employment.

Richard Doll

HENDERSON, Maureen & CURWEN, M. P. **Cancer of the Lung in South-West England and London: an Epidemiological Study of Histological Type.** *Brit. J. Cancer.* 1961, Mar., v. 15, No. 1, 19–29, 1 fig. [12 refs.]

An examination has been made of the histological diagnosis attached to 3,965 cases of lung cancer registered under the national cancer registration scheme in the south-west of England and at two London undergraduate teaching hospitals, between 1945 and 1956.

The distribution of the main histological types varied according to sex and source of material—*i.e.* autopsy, resection or biopsy. Squamous carcinomas were more common in men (49%) than in women (24%); adenocarcinomas were more common in women (20%) than in men (10%). Squamous carcinomas were the commonest type in resected growths in men (62%), but were much less common in autopsy specimens (25%). Conversely oat-cell tumours were more common in autopsy specimens in men (31%) than in resected growths (12%). These findings are in general agreement with those of other English investigators.

An unexpected finding was that oat-cell tumours were relatively much commoner at younger ages than at older. This was true for men and for women, and was true irrespective of the source of the material. It was not true for other anaplastic growths and this suggests that there is an aetiological difference between oat-cell and other anaplastic tumours.

No difference was found in the distribution of the various types among persons resident in town and in the country and there was no regular trend in the proportions with time. It is, however, impossible to draw any firm conclusions about temporal trends, as the cases examined were clearly not equally representative of all cases at different periods. *Richard Doll*

LEGUÉRINAIS, J., HABIBI, A., LAURENT, C. & MAUJOL, L. L'enquête sur le cancer au Moyen-Orient. Données épidémiologiques complémentaires recueillies en Iran. **[Cancer in the Middle East: Complementary Epidemiological Data from Iran]** *Bull. Inst. Nat. Hyg.* Paris. 1961, July–Aug., v. 16, No. 4, 669–91, 8 graphs.

In a previous paper [this *Bulletin*, 1961, v. 36, 516] the authors presented statistical and epidemiological data on 7,698 cases of cancer derived from the records of the hospitals of the Faculty of Medicine and the Institute of Cancer in Teheran. These cases were in persons who were of a medium socio-economic level and received free treatment at the hospitals.

The present paper contains an analysis of the data on 1,424 cases of cancer in persons of easy or rich circumstances from the private laboratory of the Professor of

Pathological Anatomy in Teheran. These persons were in general under the treatment of private physicians.

This detailed analysis, fully described with numerical tables and graphs deals with the general and precise localization of the tumours; their distribution by age and sex; and the frequency of the cancers according to the histologically determined nature of the tumour. The results of this analysis are compared with those obtained in the analysis, described in the previous paper, of the 7,698 hospital cases.

In the conclusions it is stated that in Iran the predominant sites of cancer are the skin, breast, the uterine cervix, the lymphatic system, the oesophagus and the larynx. Malignant disease in Iran tends also to attack at an earlier age than in western Europe but this is doubtless linked with the different age distribution of the populations. Among the differences found between the two economic classes analysed in the two papers are:—(1) cancer of the skin represented a greater percentage of all cancer cases (23%–26·8%) in the lower economic class than in the upper class (11·5%), (2) cervical cancer percentage was 10·3%–11·2% in the lower but 8·2% in the upper class, but (3) mammary cancer had a percentage of 13·8% in the upper class and 5·5%–3·9% in the lower class. *M. E. Delafield*

KREYBERG, L. **Relationship of Different Histological Lung Tumour Groups to Tobacco Smoking.** *Brit. J. Cancer.* 1961, Mar., v. 15, No. 1, 51–3, 2 figs.

The author has shown previously that the histological types of lung cancer can be divided into two principal groups, which differ in respect of the sex, domicile, occupation and smoking habits of the patients [this *Bulletin*, 1956, v. 31, 819 *bis*]. In particular an analysis of 258 male cases in Norway showed no relationship between smoking and group II cases [adenocarcinoma, alveolar carcinoma, adenoma and cylindroma] whereas there was a close relationship betwen smoking and group I cases [squamous and oat-cell carcinoma]. These findings were subsequently confirmed in a large British series [*ibid.*, 1957, v. 32, 960].

In the present paper, the author examines the ratio between group I and group II cases for different levels of smoking in 522 male patients in Norway. The ratio increased from 0·3 to 1 for non-smokers to 9·0 to 1 for men smoking more than 30 grammes a day. If the risk among non-smokers is taken to be 1, and group II cases are assumed to be unrelated to smoking, the increase in the ratio provides an estimate of the increase in the risk of group I lung cancer with an increase in the amount smoked. The results obtained by this method are closely similar to the estimated risks obtained from comparison of lung cancer and control patients in Britain.

Richard Doll

DICKENS, F. & JONES, H. E. H. **Carcinogenic Activity of a Series of Reactive Lactones and Related Substances.** *Brit. J. Cancer.* 1961, Mar., v. 15, No. 1, 85–100, 6 figs. on 3 pls. [39 refs.]

Review of 2,108 substances tested for carcinogenic activity shows that very few lactones have been tested—and these over only inadequate periods. One of the few adequately tested is β-propiolactone. This has been found to be mutagenic and has also produced sarcomas and epitheliomas in a substantial proportion of treated rats and mice.

In the present study β-propiolactone, a group of biologically active unsaturated lactones and a few less reactive lactones, have been tested by twice weekly subcutaneous injections into 2-month-old rats, until tumours developed or for a maximum of 60 weeks. β-propiolactone in arachis oil produced tumours in all rats surviving for 34 weeks, at a dose level of 0·1 mgm.—one-twentieth of that used previously. Antibiotics, patulin and penicillic acid, were carcinogenic in all rats surviving 58 and 48 weeks in doses of 0·2 mgm. and 2 mgm. respectively. Penicillin G in 2 mgm. doses produced sarcomas in 2 out of 8 surviving rats (at 72 and 84 weeks). Three synthetic unsaturated 5-membered lactones also produced sarcomas at the site of the injection.

Attention is drawn to the properties of antibiotic action and growth inhibition in this group of carcinogenic substances and the complete or partial inactivation of all of these properties by cysteine.

Two main types of chemical constitution appear to be associated with carcinogenicity in this series: a highly strained 4-membered ring or a lactone ring having double bonds at the 2 or 4 position.

[β-propiolactone has been used in the inactivation of poliomyelitis vaccine; see LÉPINE, this *Bulletin*, 1959, v. 34, 954.] *Richard Doll*

BALDWIN, R. W., CUNNINGHAM, G. J. & PRATT, D. **Studies on the Carcinogenic Action of Motor Engine Oil Additives.** *Brit. J. Cancer.* 1961, Mar., v. 15, No. 1, 123–6, 5 figs. on 2 pls.

One of the substances sold commercially for addition to motor oil to improve engine performance has been tested for carcinogenicity. 0·3 ml. of the additive was dropped onto the clipped back of each of 40 stock albino mice twice weekly for 45 weeks and spread with a glass rod; after a rest period of 5 weeks, skin painting was resumed for another 15 weeks. The first tumour was observed after 19 weeks, at which time 35 of the mice were alive. Of these mice, 6 (17%) developed benign tumours and 18 (51%) developed squamous cell carcinomas. Many of the tumours were associated with marked inflammation and (in some cases) ulceration.

The additive consisted of a Venezuelan crude oil as a base and a petroleum product containing the lead salts of a complex mixture of carboxylic acids, predominantly aliphatic in character, with a cyclopentane ring structure. Since crude oils have previously given a low carcinogenic response it is thought that the other components—particularly lead naphthenate—are likely to be carcinogenic or to act as co-carcinogens to the base oil. *Richard Doll*

See also p. 1248, WORLD HEALTH ORGANIZATION. TECHNICAL REPORT SER. No. 220, **Evaluation of the Carcinogenic Hazards of Food Additives.**

Sanitation

The order in this section is:—**General; Water and Swimming Baths; Sewage, Trade Waste and Refuse Disposal; Housing; Infestation; Atmospheric Pollution; Port, Ship and Aviation Hygiene.**

WATER AND SWIMMING BATHS

(Including the Bacteriology of Water Supplies)

MÜLLER, Gertrud. Der Enterokokkennachweis bei bakteriologischen Wasseruntersuchungen. **[Demonstration of Enterococci in Bacteriological Examinations of Water]** *Zent. f. Bakt.* I. Abt. Orig. 1961, v. 182, No. 3, 318–23, 2 figs.

The author investigated various selective media to find the most suitable for use with membrane filtration for demonstrating faecal streptococci in water samples. The media tested included 6·5% NaCl blood agar, alkali blood agar at *p*H 9·6, 6·5% NaCl. blood agar at *p*H 9·6, the Hajna and Perry S-F medium, Barnes TTC agar and the Slanetz and Bartley sodium azide TTC agar [this *Bulletin*, 1958, v. 33, 495]. The last named was found to be far the best under the conditions of the test.

By using membrane filtration in combination with sodium azide TTC agar medium it was possible to make enterococcus counts in the same way that coliform counts are usually performed. However, as the coliform count was always higher than the enterococcus count, the author concludes that the latter can only serve as a supplement and, not as a substitute for the former. Of the 3,085 strains examined 1,943 belonged to the *Strep. faecium* group and 979 were classified as *Strep. glycerinaceum* [? *faecalis*]. *E. Windle Taylor*

SKALICKÝ, J. Význam kultivační teploty pro izolaci a identifikaci některých mikroorganismů podčeledi Escherichieae z pitných vod. **[Importance of the Cultivation Temperature for the Isolation and Identification of some Micro-organisms of the Genus Escherichieae from Drinking Water]** *Československ. Hyg.* Prague. 1961, v. 6, No. 7, 402–10. [43 refs.]

The English summary appended to the paper is as follows:—

" 1. Strains of E. coli isolated from human faeces maintained their full capacity of growth and production of gas for 24 hours in a 0.5% glucose medium at a cultivation temperature up to 41° C. At a temperature of 46° C 11.0% of the strains did not produce gas and 3.0% of the strains did not produce gas or acid. 2. Among investigated strains of E. coli isolated from drinking water 6.5% did not produce gas after 24 hours at a temperature of 41° C, and 1% did not produce gas or acid, while at a cultivation temperature of 46° C 17% of the investigated strains did not produce gas and 17.5% did not produce gas or acid. 3. Strains of E. coli isolated from drinking water in the cold months of the year (October to April) began to lose capacity of growth already at a temperature of 41°C, while strains isolated during the warmer months (May to September) lost this capacity only at a temperature of 43° C in 48 hours. 4. When a cultivation temperature of 30° C was used in the cold months but in particular in the warm months, the detection rate of E. coli from specimens with a low content of a heterotropic water psychro-or mesophil microflora increased, as compared with a temperature of 37° C. 5. To obtain a maximum detection rate of E. coli microorganisms from drinking water in the winter months a cultivation temperature of the fermentation test of 30° C proved suitable, while in the warm season a cultivation temperature of 37° C is recommended. When the above temperatures were used a maximum detection of E. coli, Citrobacter and Klebsiella aerogenes was also obtained, regardless of the amount of bacteria in the water specimens."

WOODWARD, F. L., KILPATRICK, F. J. & JOHNSON, P. B. **Experiences with Ground Water Contamination in Unsewered Areas in Minnesota.** *Amer. J. Pub. Health.* 1961, Aug., v. 51, No. 8, 1130–36.

In the introduction to the work described in this paper, the authors refer to the potential health and nuisance problems which may arise when new areas are developed ahead of central services of water supply and sewerage and without adequate local control. Particular consideration is given to the situation in the metropolitan area of Minneapolis and St. Paul where " home builders have proceeded to install thousands of homes with on-site water and sewage disposal ". It was clear that with this rapid development " as the demand for water approached and exceeded the rate of groundwater recharge by precipitation " the water drawn from numerous wells " if returned to the same ground in the form of sewage, will inevitably circulate and progressively deteriorate in quality ".

Concern about this danger was expressed by the Minnesota Department of Health in 1950; warnings were given and these " proved to be prophetic " for in 1959 over 40% of the water supplies in a large suburb were found to contain " elevated concentrations of sewage chemicals ".

The survey described in this paper was carried out in the " post-war unsewered village of Coon Rapids " which had a population of over 10,000 accommodated in about 3,300 homes and business establishments. All these premises had individual sewage systems of septic-tank-soil-absorption type and most obtained water from individual wells which varied in depth from 10–100 feet.

A statistically representative number of samples (98) of water were examined for nitrate, surfactant and chloride

concentrations. The chief findings of the chemical examinations of the samples were:—(1) 62·2% contained from 1 to 21 parts of nitrate nitrogen per million and in 10·2% the concentration was 10 or more p.p.m.; it is noted that in Minnesota the natural occurrence of nitrate in more than trace amounts is not common, and (2) 23·6% of the samples contained surfactants.

There is a full description and discussion of the findings with mention of the widespread anxiety caused by them. Similar surveys undertaken in 39 other communities showed that of more than 63,000 wells involved about 47·5% were contaminated *M. E. Delafield*

PUBLIC HEALTH LAB. SERVICE. **The Detection of the Typhoid Carrier State. Report of the P.H.L.S. Working Party on the Bacteriological Examination of Waterworks Employees** [ANDERSON, E. S., Chairman]. *J. Hyg.* 1961, June, v. 59, No. 2, 231–47. [23 refs.]

This paper is concerned with a re-examination of the procedures used for the routine screening of persons employed, or about to be employed, in constructional or maintenance work of water undertakings to ensure that they are not typhoid carriers. In the main the screening consists of routine agglutination tests to determine whether the sera of such persons contain agglutinins which could be accepted as evidence of a previous enteric infection or merely evidence of immunization against these infections or whether the results suggest a typhoid carrier state. Although the agglutination tests are concerned with the detection of antibodies against all the antigens contained in the typhoid-paratyphoid organisms, particular attention is paid to the estimation of Vi agglutinins.

The Vi-agglutination test was first suggested as a suitable screening test for typhoid carriers by FELIX, *et al.*, in 1935 [*J. Hygiene*, 1935, v. 35, 421; this *Bulletin*, 1936, v. 11, (71)] and since that date an extensive literature has accumulated around the question of the importance of Vi agglutinins as an indication of the typhoid carrier state. In spite of the fact that the value of this literature is very unequal and that much is unacceptable as evidence, either for or against the importance of the test, because of the absence of adequate controls or standardized technique, it is now generally agreed that a high proportion of typhoid carriers show the presence of Vi agglutinins in their sera and that, at any rate among populations where the disease is not endemic, these agglutinins are comparatively rare in non-carriers.

The results of the investigations reported in the present paper show that 71·5% of the 67 known typhoid carriers examined had significant Vi agglutinins in their sera and that only 1·17% of the 343 normal sera tested were positive. All the tests were carried out by the fully standardized procedure routinely followed in the Public Health Laboratory Service and readings were critically assessed. Even though the proportion of known typhoid carriers with significant Vi agglutinins was lower than some other workers have reported, the high degree of specificity indicates that the test has considerable value as a screening procedure. The paper discusses a number of other matters of interest and concludes with suggestions for a revised official memorandum on the medical examination of employees, or potential employees, engaged in constructional or maintenance work of water undertakings. *H. J. Bensted*

NEWMAN, H. F. **Investigation of Acute Gastroenteritis at a Popular Resort Area.** *Pub. Health Rep.* Wash. 1961, Aug., v. 76, No. 8, 712–16, 1 fig.

Mild "enteric disorders" are "among the most common and yet the most ill-defined groups of illnesses afflicting the American people".

In late July 1959 the Seattle-King County Department of Public Health were notified of the occurrence of acute gastroenteritis in 7 of 12 members of a family after a picnic at a well-known resort. A few days later an explosive and severe outbreak of gastroenteritis affecting 29 of 36 members of a girls' club following an outing at the same resort was reported. Thereupon a detailed investigation was undertaken by the health department. Enquiries revealed that, in all, at least 58 people who had visited the resort in late July had had gastroenteritis.

There is a map of the resort area and a description of the facilities provided. The water supply which came from 2 shallow wells was "highly suspect because of well construction, positive coliform counts, and reported bad odor and taste of the water".

From the findings of the investigation which included careful questioning of the sufferers "it is reasonable to infer from these data that water from well 2 was the vehicle of disease transmission".

"Determination of the true etiological agent in these illnesses cannot be made at this time" but on examination of stool specimens from 4 members of the girls' club ECHO 9 virus was grown on tissue culture from 2 specimens. *M. E. Delafield*

SANI, A. Riscaldamento domestico dell'acqua: effetto sulla carica batterica. **[The Effect of Heating of Water in the Home on its Bacterial Content]** *Igiene e San. Pubblica.* Rome. 1961, May–June, v. 17, Nos. 5/6, 267–75. English summary.

Following some general considerations on the possible results of heating, in the house, water intended for drinking or for culinary uses, the author describes the effect on the bacterial flora of water heated (1) by electrical devices, and (2) by using the central heating apparatus. 10 examinations were made in each case, the temperature reaching an average of 87·7°C. in the first and of 50·8°C. in the second. None of the water samples contained presumptive *Escherichia coli* in 100 ml. initially. In all cases there was a varying fall in the count on agar at 37°C. and in that on gelatin at 20°C. The number of samples was, of course, small, only the examinations referred to were done, and this note is only presented to draw attention to a point of domestic hygiene which is said not to have hitherto received much study.

E. Agius

ATMOSPHERIC POLLUTION

EVELYN, John. **Fumifugium: of the Inconvenience of the Aer and Smoake of London Dissipated.** 41 pp., frontispiece. First published in 1661 and reprinted 1961. London: National Society for Clean Air, Field House, Breams Buildings, E.C.4. [2s. 6d.]

The feeling in the air in England in 1661 must have been very like that in 1946: after a long period of trial and tribulation (for the Commonwealth in its latter days had had very few supporters) the country was at the beginning of a new era. As in 1946 however there was no general agreement on aims. Some hoped for a return to the Good Old Days, some only for stability and peace, and to some like John Evelyn there seemed the opportunity for a national renaissance, so that he could write: "we may promise ourselves not only a recovery of our former Splendor; but also whatever any of our Neighbours enjoy of more universal benefit, for Health or Ornament: In summe, whatever may do honour to a Nation so perfectly capable of all advantages".

Fumifugium may be regarded as part of a blueprint for this Brave New World. It shows however that Evelyn, far from being an abstract visionary, was an astute observer and a worthy founder member of the Royal Society. He puts his finger unerringly on the main causes and worst effects of "that infernal Smoake", and when his conclusions differ from ours it seems likely that the differences are due to real changes since his day.

The smoke which he found so obnoxious was that of "Sea-Coale", which must have been produced copiously in fire-places and furnaces intended for burning wood. At that time and in the following half-century scarcity of timber was forcing industry to turn from wood to coal for fuel, and one of the few mistakes Evelyn makes in this essay is in suggesting that enough wood could be obtained. He regards industry—"*Brewers, Diers, Limeburners, Salt* and *Sope-boylers*, and some other private Trades"—as the chief cause of the nuisance, as it probably was in his time, and takes it for granted that London is very much worse afflicted by smoke than any other city in Europe. In this also he is almost certainly right, since he and many of the other Royalists among whom he moved and "who (during these sad confusions) have been compelled to breath the *Aer* of other Countries for some years" had had opportunities to see for themselves. Moreover, London at that time was the only large town in Europe which depended on coal to any great extent.

The style of writing is that of a more leisured age, interlarded with meandering speculation and classical allusion, but it maintains our interest by the vivid vitality of such phrases as "that Hellish and dismall Cloud of SEA-COALE", and by the fascination of searching in vain for effects which Evelyn missed. To readers of this *Bulletin*, with the 1952 London fog in mind, perhaps his most evocative sentence will be: "But how frequently do we hear men say (speaking of some deceased Neighbour or Friend) *He went up to* London, *and took a great Cold, &c., which he could never afterwards claw off again*?"

The National Society for Clean Air must be congratulated on having reprinted this classic, and at such a reasonable price. *John McK. Ellison*

RUMFORD, J. **Mortality Studies in relation to Air Pollution.** *Amer. J. Pub. Health.* 1961, Feb., v. 51, No. 2, 165–73, 5 figs.

In this paper the author tries to show how a comparison of mortality in different districts of large towns with corresponding measurements of air pollution can be used to study the effect of atmospheric pollution on health.

The data discussed first are from Philadelphia, for which the only figures of air pollution available for all districts are those giving dustfall in 1958. Linear correlations between this and the mortality from various diseases for the years 1954–6 were calculated, and also "correlation matrices" between mortality, dustfall and four "indexes of socioeconomic level of the health district". Only chronic rheumatic heart disease seemed more strongly related to dustfall than to the social factors.

The second study concerns Chicago, and to ensure that the population investigated spent most of their time near their homes this study was confined to white women. Three investigations were attempted. Firstly manufacturing and non-manufacturing areas were compared by pairing districts which were socially and economically similar but differed in the extent of industrialization. As might be expected the mortality in industrial districts was higher. The second comparison was of the mortality within one mile of a large metal-producing plant with that between one and two miles from the plant, and in the third the mortality in the districts to which the prevailing winds blew the pollution were compared with that in districts which were not in general to the leeward of the sources.

Finally there is a brief description of what the author calls the "temporal study", in which day-to-day figures of deaths are plotted on the same graph as air pollution data, and fluctuations compared.

[The methods described are interesting, but the description is too cursory and the consideration of the interplay between different factors too slight for the paper to be of any real value.] *John McK. Ellison*

CIOCCO, A. & THOMPSON, D. J. **A Follow-up of Donora: Ten Years after: Methodology and Findings.** *Amer. J. Pub. Health.* 1961, Feb., v. 51, No. 2, 155–64, 1 fig. [11 refs.]

Immediately after the 4 days of acute air pollution at Donora, Pennsylvania, in October 1948 [this *Bulletin*, 1950, v. 25, 392] the U.S. Public Health Service carried out a survey of one-third of the households in the borough. In the 1957 survey (which was in fact not 10 but only a little more than 8 years after) the authors claim to have traced over 99% of the 4,092 residents in the original sample—an astonishing feat.

The original sample has been split up into categories according to age, sex, and illness reported in 1948, and the morbidity for various diseases and the mortality for each category in the intervening period are given. Under each heading however the numbers are very small and the information obtained must be treated with reserve even when (for example) what seems to be the death of 5

people out of 19 is disguised as a mortality rate of 263 per 1,000 population (table 2). No statistical tests have been applied at all, and the authors' claims that "the essential findings of this investigation are that persons who reported acute illness at the time of the smog episode have demonstrated subsequently higher mortality and prevalence of illness than the other persons living in the community at that time", and, "furthermore, persons who complained of more severe acute illness in 1948 demonstrate greater subsequent morbidity and mortality than persons with mild complaints" must be regarded as unproven. *John McK. Ellison*

i. HARRIS, W. J. **Method for Size-Distribution Determinations of Non-Volatile Droplets by Electron Microscopy.** *Brit. J. Applied Physics.* 1959, Mar., v. 10, No. 3, 139–40, 2 figs.

ii. ——. **Size Distribution Determinations of Non-Volatile Droplets by Light and Electron Microscopy.** *Ibid.,* 1961, July, v. 12, No. 7, 348–9, 2 figs.

i. In the method described in the first of these two papers the droplets (which must not be miscible with water) are sampled on a wet gelatin film, on whose surface they produce impressions. These remain when the film is dried and the droplets are washed off. Standard electron microscope techniques are then used to get shadowed replicas of these impressions, which are sized by electron microscopy. The corresponding droplet radii are obtained by multiplying by a calibration factor, which is based on measurements by optical microscope with very much larger droplets of the same substance.

ii. In the modification described in the second paper the sample is deposited on a dry gelatin film; this permits a considerable wider choice of sampling instruments. After sampling, the gelatin is moistened by breathing on it, and the depressions produced are measured in the same way as before. *John McK. Ellison*

PEMBERTON, J. **Air Pollution as a possible Cause of Bronchitis and Lung Cancer.** *J. Hyg., Epidemiol., Microbiol. & Immunol.* Prague. 1961, v. 5, No. 2, 189–94, 4 figs. & 1 graph.

Daily measures of air pollution—amount of dark smoke and amount of acid gas (mainly sulphur dioxide)—have been made in the City of Sheffield at some 30 points. On two occasions when a sudden rise in pollution was recorded there also occurred a marked increase in the illness reported by a group of men suffering from chronic bronchitis and in the number of new attacks of bronchitis registered in the whole male working population. There is also an excess of deaths from bronchitis and from lung cancer in those areas of the city which are most polluted. This association, however, disappears when allowance is made for the concomitant geographical distribution of such social factors as housing density, type of occupation and social class. It is concluded that these observations and those of other workers [this *Bulletin,* 1959, v. 34, 1144] strongly suggest that air pollution is one of the causes of exacerbations of and deaths from bronchitis; it may also be one of the causes of lung cancer but the evidence for this is not conclusive.

Austin Bradford Hill

SCHREIBEIS, L., Jr., GROVE, J. J. & DOMKE, H. R. **Air Pollution Control in Urban Planning.** *Amer. J. Pub. Health.* 1961, Feb., v. 51, No. 2, 174–81, 1 fig.

For the most part this a short description of the way in which Pittsburgh and Allegheny County have been able to achieve the dramatic reduction in air pollution over the past 20 years, of which they are so justifiably proud. In bringing about this improvement changes in technology and in economic conditions and also legislation have played their part, and this interesting paper gives a brief account of how the various factors affected one another.

John McK. Ellison

Occupational Hygiene

The order in this section is:—**General; Occupational Physiology; Occupational Diseases (Dust Diseases, Poisoning, Skin Diseases, Others); Occupational Psychology; Heating, Lighting and Ventilation.**

GENERAL

PROC. FOURTH CONFERENCE INDUST. COUNCIL FOR TROP. HEALTH sponsored by the Harvard School of Public Health, July 20–22, 1960, in Boston. **Industry and Tropical Health, IV.** 311 pp., numerous figs. 1961. Boston: Harvard School of Public Health, 55, Shattuck Street, Mass., U.S.A.

Like its predecessors, this volume is handsomely printed and illustrated, largely by photographs of participants at the conference, but also by technical photographs and text figures, which all help in understanding. Photographs of the participants bring a refreshing touch of intimacy, which is also a help.

Many of the papers are summaries of modern information on the subjects with which they deal, and most of them are masterly. Conferences do not provide the proper milieu for the announcement of new discoveries, and therefore these summaries are appropriate to the occasion, especially if they are combined with an expert evaluation of trends and a critical evaluation of importance to the subject in hand. On this point some of the

principal papers are open to criticism; they state the position but they do not always, or sufficiently, discuss the implications. On the other hand the discussions which follow the papers, and which are very fully recorded, usually bring out the salient and important points with clarity and force.

The first session was notable for a thoughtful article by A. GABALDÓN (pp. 14–28) who from his great experience in Venezuela, during the period when he directed the antimalaria campaign and saw the introduction of the new insecticides and drugs, draws the conclusion that the enormous changes brought about in the health conditions of the people have so affected the social structure that the old conventional western approach to health in developing countries must be changed to meet the new situation. It is not enough to imitate the advanced communities—a point emphasized in discussion by G. GIGLIOLI (p. 33) who comments on "the paramount importance of ecology in the teaching of public health for tropical areas".

In the second session speakers discussed the responsibilities of various agencies—management, government, labour, local communities—for health services in developing areas, but some related to industry and local communities in the United States itself, that is, they were not specifically tropical. These papers are largely concerned with the administration of health services.

At the third session J. H. S. GEAR gave a comprehensive account of schistosomiasis (pp. 86–101), mentioning infection of man by *Schistosoma mattheei*, essentially a parasite of bovines in South Africa. Other speakers discussed control by molluscicides, manipulation of water, and biological methods, and the present status of treatment. These are all admirable summaries of current knowledge. Gear made the point that in Africa, where so many people harbour these parasites, the opinion has grown that infected persons do not necessarily have serious disease, but after detailing the possible effects of the infection he combats this view—"Such a disease is no minor problem".

The fourth session related to trachoma and recent clinical and virological research. P. THYGESON (pp. 132–141) commented that "There is now no difficulty in treating individual cases of trachoma with sulfonamides or antibiotics, or with a combination of the two, but treatment times are still too prolonged for satisfactory mass treatment campaigns". But intermittent short treatment schedules are effective for schoolchildren and may be more popular than continuous schedules. These papers are highly informative.

Oral immunization against poliomyelitis was the theme of a paper by A. M.-M. PAYNE (pp. 154–163), who provided an excellent account of the subject, ending on a hopeful note. G. A. MYERS (pp. 167–172) described the epidemiology of epidemic cerebrospinal meningitis in Nigeria and Ghana, drawing largely on the work of B. B. WADDY, who related the disease to climatic factors which in turn affected human behaviour and produced conditions favouring rapid spread—a fascinating epidemiological study. R. S. F. SCHILLING (pp. 172–173) briefly discussed the teaching of occupational health, with emphasis on the need to allow students to participate in the course rather than to expect them only to sit and be taught.

The fifth session opened with a paper on tropical eosinophilia by P. C. BEAVER (pp. 176–182), and this was followed by papers on the control of flies and anophelines, with considerable detail of fly control at a station of the Arabian American Oil Company on the Persian Gulf, by R. L. PEFFLY (pp. 186–196). A. W. A. BROWN (pp. 197–205) dealt broadly with anopheline resistance to insecticides.

The sixth session was devoted to viruses important in the tropics, including the influenza viruses. F. M. DAVENPORT (pp. 211–219) ended his contribution:—"In summary, the threat of influenza is ever present and the visitations are costly. The record of the efficacy of vaccination is excellent . . . I would like to conclude with a challenge, 'In view of this information, can you as industrial physicians, justify to your firms a health program that does not include annual protection against influenza by vaccination?'"

The final papers were on the arthropod-borne viruses and the ECHO viruses; both were excellent and informative summaries.

The reviewer is left with a feeling of admiration for a series of papers well written and highly competent to explain their subjects, but also with a feeling that many of these subjects were approached from a universal rather than an industrial point of view, and to this extent the conference seems to have strayed from its terms of reference. Industrial development is so important in the tropics that the reviewer would have welcomed much more first-hand information on its effects on health and social structure, and on the means taken to cope with it in actual practice. *Charles Wilcocks*

BRUNO, L. La schermografia nell'industria. Risultati di nove anni di indagini in una industria metalmeccanica. [**Miniature X-Rays in Industry**] *Med. d. Lavoro.* 1961, Mar., v. 52, No. 3, 191–5. [22 refs.] English summary (8 lines).

Mass radiography is a potent weapon in the prevention of tuberculosis but it loses much of its effectiveness unless practically the whole of the population invited to participate is in fact examined by X-ray and the response is likely to be greater if surveys are limited to compact homogeneous groups. The author describes his experience in an engineering works and he stresses the importance of the right approach to the workers, which should include an assurance that information gained as a result of examination will be regarded as a matter of confidence between worker and works doctor. The findings for 6 years in the period 1952 to 1960 inclusive are given in a table and the response rate even in the earlier years was 93 to 94% and rose subsequently to 98 to 99%. In 1952 active tuberculous lesions were found in 0·302% of those examined by X-ray which is about the same level as that generally met with in Italy, but by 1954 they had fallen to 0·177% which compares well with findings in England and in Argentina where periodical surveys are made by mass miniature X-rays. Finally in 1960 active tuberculous lesions accounted for only 0·045% of cases examined.

These results serve to indicate the contribution that a works medical service can make to the practice of preventive medicine provided it has the tools needed to carry

out a programme in accordance with modern views on hygiene and occupational health. *G. F. Keatinge*

ADELSTEIN, A. M. **Death and Serious Disease in White Railwaymen of the South African Railways.** *Med. Proc.* Johannesburg. 1961, July 15, v. 7, No. 14, 286–99.

This paper contains a detailed analysis of the incidence and causes of death and serious chronic disease among white railwaymen of the South African Railways in the quinquennium 1954–59, who numbered about 95,000. It is based on data from records of the South African Railway Superannuation Fund and on sickness absence and other administrative records.

The findings of the review are well described and discussed. There is an appendix containing 15 tables of detailed statistical data.

The main causes of death were arteriosclerotic and degenerative heart disease (30%) which conditions were also the main reason for retirement. Accidents (25%) and malignant neoplasms (12·5%) were the next most frequent causes of death. No significant differences in death rates due to the heart diseases were found between the "white collar" and "physically occupied" groups of railwaymen, or between these death rates and those of "all South African males which are among the highest when countries are compared". Accidents were an important cause of death and among the physically occupied group caused more deaths than did arteriosclerotic heart disease. It is to be noted that the "physically occupied group have more deaths from accidents while not at work than from accidents at work".

Pulmonary tuberculosis is still a serious cause of illness. During the 5 years 207 cases became known with an increase in age incidence from 20 cases per 100,000 at age 15–25 years to 104 at age 55–65 years.

M. E. Delafield

BECKER, W. & MATZKER, J. **The Acoustic Accident.** *German Med. Monthly.* Stuttgart. 1961, June, v. 6, No. 6, 191–94, 196, 4 figs. (1 on pl.) [13 refs.] [Translated from *Ztschr. f. Laryngol. Rhinol.* 1961, v. 40, 49.]

Two cases are reported, where one man of 56 and another of 35 years of age were separately exposed to the noise from a circular-saw for a period of one-half to three-quarters of an hour for the purpose of domestic wood-cutting. Subsequently they suffered loss of hearing, which remained for the period of observation of 8 to 18 months. The overall sound pressure levels during sawing were in the range 90–115 db.

The older man had a previous history of progressive perceptive deafness in the left ear, but the right ear had been normal. Subsequent to exposure, the right ear showed fairly uniform loss of about 70 db, and the left ear showed an average loss of 85 db, with more marked loss at the lower frequencies.

The younger man's audiogram showed a perceptive loss, more severe in the right ear than the left, with dips of 85 and 60 db respectively at 1,000 cycles per second.

The authors suggest that these patients, together with 2 others recorded in the literature, suffered a spasm of the labyrinthine vessels as a result of sudden and intensive exposure to loud noise, continuation of which increased and sustained the spasm. It is postulated that the resultant circulatory disturbance led to a circumscribed labyrinthine hydrops confined to the cochlea, and not involving the semi-circular canals. An aggravating factor is considered to be a temporary faulty posture of the cervical spine through exaggerated flexion while bending over the saw. A special pre-disposition of the labyrinthine vascular system is thought to have been present, making an originally reversible lesion irreversible after a short exposure to noise.

The incidents are classed as cases of accident rather than of occupational disease. *D. E. Hickish*

MILIJIC, B. A propos d'un cas neurologique de la maladie des caissons. [**A Neurological Case of Caisson Disease**] *Med. d. Lavoro.* 1961, Mar., v. 52, No. 3, 205–9.

The clinical history of a case of caisson disease occurring in a young man of 21 years is described in detail. In 1957 following work in a caisson at a pressure of 2 atmospheres, he went through the ritual of decompression but 20 minutes later began to experience great pain in the legs accompanied by paraesthesia rendering movement impossible and respiration difficult. Half an hour later he had improved somewhat but the condition was not recognized as caisson disease and he was not sent back to the recompression chamber. Improvement did not take place and he was admitted to hospital: he remained very ill and a few days later was transferred to a neuropsychiatric clinic. He was regarded as a case of transverse myelitis and was later sent to a rehabilitation institute where the condition was recognized for what it was. Some improvement took place but on re-examination 2 years after the original episode he could walk only with difficulty, remained severely disabled and in general his state was progressively deteriorating.

The author comments that if the nature of the symptoms had been recognized sooner and the patient put back into the recompression chamber immediately the complications which followed might not have been so severe. It is added that decompression is very often not conducted with enough care since there are an insufficient number of men trained to carry out this technique. The suggestion is put forward that the clay strata on which the caisson was placed contained decomposing materials and that noxious gases given off from it may also have played some part in causing the widespread damage which resulted in this case: it is said that given the same atmospheric pressure such severe effects would not have followed if the site had consisted of sand or stone.

[British Regulations are stringent and amongst the requirements it is laid down that "Every man lock shall . . . be in charge of a competent lock attendant". Whatever the nature of the geological stratum upon which

the caisson is sited there is no doubt that careful and competent decompression is the major factor in preventing the onset of caisson disease.]

G. F. Keatinge

MAGNUSON, H. J. **Recent Developments in Occupational Health in the United States.** *Ann. Occup. Hyg.* London. 1961, Sept., v. 4, No. 1, 1–18. [Numerous refs.]

OCCUPATIONAL PHYSIOLOGY

BALGAIRIES, E., AMOUDRU, C., MASURE, P. E. & QUINOT, E. Étude corrélative des débits expiratoires et de la vitesse expiratoire mesurée au "Peak Flow Meter". [**Study of the Correlation between the Peak Flow Rate and the Forced Expiratory Volume and the Maximum Voluntary Ventilation by Means of the Peak Flow Meter**] *Rev. Méd. Minière, Sin-le-Noble.* 1960, v. 13, No. 41, 24–32, 3 figs. & 2 charts.

This article first reviews publications dealing with performance and limits of normal of the "Peak Flow Meter" of WRIGHT and MCKERROW [this *Bulletin*, 1960, v. 35, 850]. There is a fall with age from 585 to 304 litres per minute over the age range 25–65 according to HIGGINS [*ibid.*, 1958, v. 33, 238].

Peak Flow Rate (PFR) has been compared by the present authors with Forced Expiratory Volume (FEV) and with Maximum Voluntary Ventilation (MVV) (direct) in 352 patients in a sanatorium who were mainly suffering from tuberculosis (257) and pneumoconiotuberculosis (81). Against FEV, PFR gave a correlation of 0·92, and 70% of the observations lay within ±0·350 litre of the regression line. Against MVV direct the correlation was 0·90. Here the variation was unequal throughout the range so that at 625 litres PFR, 12% of subjects would have an MVV departing by more than 18 litres from the value predicted from PFR, whereas at 250 litres PFR, 35% of subjects would show as great a departure from the directly measured MVV. Thus under 300 litres per min. PFR, the value of MVV cannot be predicted with certainty (*avec sécurité*).

It is concluded that the standard spirographic test is preferable for hospital or medico-legal practice where important decisions have to be based on the result. The PFR is well adapted to field surveys where the high correlations permit accurate estimations of the mean FEV and MVV of any population.

M. L. Thomson

OELBRANDT, L., PATIGNY, J. & LAVENNE, F. Étude de la mixique pulmonaire au moyen du nitrogenmeter. Analyse des méthodes utilisées. [**Nitrogen Meter Study of the Mixing of Inspired Gas in the Lung**] *Rev. Inst. Hyg. des Mines.* Hasselt. 1960, v. 15, No. 3, 59–78, 11 figs. [28 refs.]

This paper sets forth at greater length than is customary the steps leading to the calculation of indices of mixing of inspired gas in the human lung, in which the standard method where nitrogen is continuously measured during the wash-out of lung gas by oxygen is used. If it is assumed that inequality of ventilation is "parallel" in type (the authors point out that series inequality would also explain many of the known features of ventilatory function), it is possible to ascertain the number of units ventilating in parallel, their volumes and the extent to which each contributes to the total ventilation. The "mean actual number of respirations during which nitrogen remains in the lung" is first calculated and this is compared with the corresponding "ideal number of respirations" to give the "index of delay in pulmonary clearance" of nitrogen. Here the actual ventilation found is compared with the best possible ventilation based on the lung volumes, tidal air, dead space and rate of respiration of the person under test.

It has been proposed that indices of pulmonary clearance delay of less than 70% should be regarded as abnormal.

An extensive theoretical treatment of this subject is also given in which a modification of FOWLER's method (*J. Appl. Physiol.*, 1949, v. 2, 283; *J. Clin. Investigation*, 1952, v. 31, 40) is proposed for the calculation of the volumes of the regions which are ventilating at different rates.

M. L. Thomson

OCCUPATIONAL DISEASES

NATIONAL COAL BOARD. **The Relation between Pneumoconiosis and Environmental Conditions. An Analysis of the Results of the First Series of X-Ray Surveys in the National Coal Board's Pneumoconiosis Field Research** [HICKS, D., FAY, J. W. J., ASHFORD, J. R. & RAE, S.]. pp. viii + 42, numerous pp. of tables, 4 diagrams, 1 map & 23 figs. (22 folding). [24 refs.] 1961. London: Nat. Coal Board (Pneumoconiosis Field Research), Hobart House, Grosvenor Place, S.W.1.

The terms of reference of the National Coal Board Field Research were "to determine how much and what kinds of dust cause pneumoconiosis and to establish what environmental conditions should be maintained if mineworkers are not to be disabled by the dust that they breathe during the course of their work". In order to carry out this task 26 collieries with a wide geographical distribution, which it was considered would cover the whole range of environmental conditions in British coal mines, were chosen for investigation. The assessment of

environmental conditions was made on a "factorial" design with 4 factors each at 2 levels: (i) the dust concentration at the coal face on the coal-getting shift, (ii) the average ash content of the coal seams excluding the free dirt, (iii) the quartz content of the roof and floor strata, (iv) the rank of coal in the seams worked which was determined according to the National Coal Board system of classification. In this system the coal is described in terms of its behaviour as a fuel and as a basic material for the manufacture of gas and coke, thus anthracite is relatively low in volatile matter and high in rank (100–600) while the reverse is true of coals at the other end of the scale (700–900).

There were 34,700 men working at the 26 collieries at the time of the medical surveys and only 5% failed to present themselves for examination. Working histories were taken and the men were classified into two main groups: (i) those who had worked mainly at the pit in question (pit pure), (ii) those with a mixed pit history (pit mixed). All men in addition had their histories expressed in terms of the periods spent in each of 6 types of general environment which are indicated. The categories of pneumoconiosis used by the National Coal Board Field Research up to 1959 were those proposed by the ILO in 1953 and it was on this basis that the interpretation of the films reported in this survey was made; the film reading was rigidly controlled and formed the sole criterion of assessment of the prevalence of pneumoconiosis.

Wide variations in the prevalence of both simple pneumoconiosis and complicated pneumoconiosis or PMF were noted from colliery to colliery but there were regional similarities. Thus, the prevalence of Category 1 or more pneumoconiosis was uniformly high in South Wales, exceeding 26% at each of the 6 collieries, and also relatively high in Durham. But there are also regional variations; for example in Scotland the prevalence varied between 5·3% and 23·5% in different collieries. The prevalence of PMF varied greatly but was significantly greater in South Wales than elsewhere. The prevalence of pneumoconiosis increased fairly steadily with age, although regional differences were also noted in this respect: thus in South Wales appreciable percentages of the younger workers had Category 1 or more pneumoconiosis while in Scotland the prevalence only began to be significant in the 46–50 age-group, but on the other hand the rate of increase with age was steeper. Pneumoconiosis was found among men engaged in all types of work, although the proportion of face workers is on average only slightly higher than others employed underground. The prevalence of PMF tended to increase *pari passu* with simple pneumoconiosis and in all parts of the country, and, in all except 3 collieries, was approximately one-third of the proportion of men with category 2 or more pneumoconiosis.

None of these results threw any light on the past hazard of different occupations and working places and it was accordingly necessary to develop mathematical models which would enable this to be done. These methods are described. Since the amount of abnormality present in the radiograph increases with increasing amounts of dust retained in the lung, the most convenient form or relationship between abnormality and exposure, for analysis of the type required, is a straight line and the choice of scales is indicated. It is shown that dosage can best be measured on a logarithmic scale and although true values of abnormality and dosage are not known exactly it was nevertheless assumed that this was the case in the construction of the basic model; if the errors are made without bias and follow a Gaussian distribution the basic abnormality exposure relationship remains essentially unchanged. The rather complex mathematical implications are considered in detail and it is held that comparatively simple analyses in terms of a single measure of exposure are of limited use and a multi-dimensional method was devised to take account of the man's exposure at two or more distinct levels of the hazard. By this method it was possible to demonstrate that in general there was little difference between the past hazard at the selected collieries and that at other collieries at which the men had worked in the past. However, the comparatively small numbers at any one colliery reduced the value of the observations and as the results obtained at collieries in the same locality were similar and since it was also clear that the major hazard was associated with coal getting and that in addition there was a strong association between rank of coal and hazard, it was decided to pool data from collieries in the same area where past hazards had been similar. Standard one-dimensional analyses were applied to as many of the data as proved suitable, and by using the multi-dimensional method to analyse the data for the whole population under examination the hazard associated with the 3 most important types of environment, *i.e.*, coal-getting shift, preparation shift, and elsewhere underground, were determined. The main differences were for the coal-getting shift and the greatest hazard was at the high-rank collieries. Further multi-dimensional analyses were carried out after regrouping of the collieries on the basis of 3 broad rank of coal groups, high, medium and low, and in all three rank groups it was found that the past hazard at the coal face had been appreciably greater than elsewhere underground.

Other conclusions which emerged were the comparatively small degree of risk associated with surface work, whether dusty or not. Ripping was found to be less hazardous than coal getting and haulage work considerably less hazardous. Curiously, the hazard associated with hard heading worked out on average for the country as a whole at less than that connected with coal getting at high-rank collieries. Although the effect of rank is clear the mean of the average dust concentration over the past 7 years as measured by the PFR at high dust collieries was 410 p.p.cc. and at the low dust collieries 180 p.p.cc.; the corresponding mean dust concentration at the high-rank pits has been about 300 p.p.cc. and at the low rank pits 250 p.p.cc., which if it is representative of conditions in the past is unlikely to explain the wide difference in past hazard. As the authors say "This implies that either the relative levels of the dust concentrations were greatly different in the past from what they are now, or else some other factor than quantity must be very important". Moreover although the factorial design did not show any significant effect on the past hazard in terms of ash in seams and quartz in roof and floor, this does not mean that the total mineral content of the respirable dust and the quartz content of the dust are not significant.

Finally the overall prevalence of pneumoconiosis and

the relative dust hazards in the various coalfields of Great Britain are interpreted in the light of the results of this investigation. The opinion is expressed that " on the evidence of this investigation one would expect current prevalence and past hazard in Western Europe to be comparable with what is found at the high-rank collieries of this Research ".

[A meticulous study admirably presented and illustrated by a profusion of maps, tables and figures. The scope of this important research is too wide to allow of adequate abstracting and it should be regarded as required reading in the original for all workers in this field.]

G. F. Keatinge

LIDDELL, F. D. K. **The Effect of Film Quality on reading Radiographs of Simple Pneumoconiosis in a Trial of X-Ray Sets.** *Brit. J. Indust. Med.* 1961, July, v. 18, No. 3, 165–74, 2 figs.

In June 1955 1,400 men had been examined by X-ray at Chislet Colliery in Kent and for the present trial 100 subjects were chosen from the men known to be still employed at Chislet, to include a high proportion with evidence of pneumoconiosis and particularly of those whose films had been read differently on two separate occasions by a single observer. 87 men attended but one film was blank and accordingly only 86 subjects were investigated. The main intention of the trial was to compare chest X-ray films (14″ × 14″ postero-anterior) taken on 4 different X-ray sets in order to assess the quality of film and to read them all for pneumoconiosis. Every effort was made to ensure uniform conditions and full details are given in the text and in an appendix to the paper.

The chest thickness was measured in cm. at maximum inspiration at the nipple level by one observer and the films were read by 6 experts. Each assessor interpreted each film independently and recorded for each film his opinion of its quality from the point of view of reading pneumoconiosis in 3 arbitrary categories, +1, 0, −1, representing above average, average and below average respectively, and on this basis all the observers regarded the films produced by 2 of the X-ray sets as outstanding. In addition 2 readers read the films on two separate occasions and thus for each of the 344 films there were 8 assessments of quality and 8 readings of pneumoconiosis. A " Quality Score " was obtained for each film by adding together the 8 individual assessments, and roughly half the films had quality scores of 0 or better which were defined as " Acceptable," and the other half had scores of −1 or worse and were classified as " Poor ". Similarly a " Pneumoconiosis Score " was obtained for each subject by adding together the 32 readings for each subject unless any of the readings was of PMF. A pneumoconiosis score of 0 means that all 32 readings were normal while a pneumoconiosis score of 48 could mean that half the readings were category 1 and the other half category 2.

A comparative table shows the observed and the expected distribution of subjects according to the numbers of acceptable or poor films and there is a clear tendency for many more subjects than expected to produce either 4 " Acceptable " or 4 " Poor " films. This result is highly significant and it is concluded that the quality of the film depends to a considerable extent on the subject. Within each pneumoconiosis group a relationship was found between a subject's chest thickness and the average " Quality Score " of his four films.

The effect of film quality on reading pneumoconiosis was also studied. Although individual readers varied considerably, on average slightly more abnormality was read in films which were too black than in the best films of the same subjects and the opposite was noted in the films which were too grey. These findings were not obviously in line with those reported in an earlier study by FLETCHER and OLDHAM [this *Bulletin*, 1949, v. 24, 971] and also by WISE (1959: Personal communication). In their series Fletcher and Oldham found that more were on average in the " expected " division (*i.e.* more abnormality was read in grey films and less in black) while in this study the tendencies were if anything reversed. Wise assumed that the real distribution of abnormality (*i.e.* what ought to be read on perfect films) would be independent of film technique but this assumption is not supported by the present results. However, the sample of films considered was biased in more than one respect, and since it was found that films which were easiest to read were generally assessed as of good quality there may be considerable inaccuracy in such subjective assessments of quality.

Perhaps the most important of the conclusions which were reached is that the quality of the film depends on the subject: chest thicknesses have an important effect on the average equality of the films and in cases where it is difficult to get technically good films the accuracy of reading of pneumoconiosis suffers most. This paper underlines the great difficulty in obtaining satisfactory radiographs in some people, whatever the apparatus used and however good the technique. *G. F. Keatinge*

CARNEIRO, S., LEANDRO, C., ALVES, C., PEREIRA, R., BESSA, S., CANTEIRO, C., RODRIGUES, A. & ANDRADE, C. Inquérito preliminar sobre a silicose em minas por radiofotografia. **[Preliminary Enquiry into Silicosis in Mines by Radiography]** *Bol. Serviços de Saúde Pública.* Lisbon. 1960, Apr.–June, v. 7, No. 2, 143–63.

This report is published by the Portuguese Ministry of Health. It opens with an explanatory note by the Director of Technical Services of the Division of Occupational and Industrial Hygiene in which he states that owing to lack of information about the extent and importance of pneumoconiosis in Portugal this preliminary enquiry was initiated, despite the fact that few people technically qualified were available and laboratory facilities were also inadequate.

The report proper begins with an introduction in which accepted present-day views on the aetiology, prevention and complications of silicosis are outlined. This is followed by a description of the apparatus and techniques used with possible sources of error which may have been present, and this section of the report is most frank and there is no doubt that many difficulties were encountered. The investigation was limited to miniature radiography (70 mm. × 70 mm.) and the X-ray examination had to be done on the apparatus available in different parts of the

country which varied greatly; thus in the south an Odelca camera was used in conjunction with an apparatus having an output of 50 mA while elsewhere cameras of the Bouwers type had to be employed and in this case the output ranged from 50 mA to 30 mA. In addition the films taken in the various regions were read by different observers who did not have an opportunity of consulting together. The authors are very conscious of these deficiencies, and since in addition it was not possible to guard against observer error (which they deplore), they are of opinion that the number of films held to show evidence of pneumoconiosis may have been lower than was actually the case.

The results are presented in a series of tables and are analysed and discussed in a separate section. 14,835 persons at 57 mines were examined by X-ray and 484 cases of silicosis were discovered (3·26%). Silico-tuberculosis and active tuberculosis occurred in percentages of 0·26 and 1·97 respectively. The number of men with silicosis working underground varied greatly in different mines, ranging from 36·7% to 0·44%, and there were also considerable regional differences: for example in the central zone the highest percentage found among underground workers was 3·33% while in the southern zone it was 36·37%. There were similar variations in the prevalence of silicosis among surface workers which reached a maximum at 8·08% and a minimum at 0·65%: regional differences were again marked and as in the case of the underground workers very low figures (2·67%) were reported from the central zone while the percentage was 8·08 in the southern zone.

The general principles in the control of silicosis are clearly well understood in Portugal and the object of this enquiry, which has been to make a preliminary exploration of the matter, has shown that an appreciable number of men with silicosis and tuberculosis are indeed working in the mines of the country. Thus there is a great need for adequate measures of prevention to be undertaken and great emphasis is laid on the lack of adequate occupational health services for this purpose. *G. F. Keatinge*

Abe, J., Morimoto, S. & Yamashita, N. **[Surveys on Silicosis in Kyoto Prefecture]** *Japanese J. Nation's Health.* 1961, Mar., v. 30, No. 1, 40–52, 7 charts. [In Japanese.]

The English summary appended to the paper is as follows:—

"Surveys based on the Silicosis Act were carried out including 3,423 workers belonging to 358 factories from 1955 to 1958 in Kyoto Prefecture. The results were as follows:

"(1) Among 3,423 workers, 540 cases of silicosis were found, and the morbidity rate 15.78% was considerably higher than that of all Japan (11.43%).

"(2) The morbidity rates in the following industries were over the average rate in Kyoto prefecture; 35.17% in the quarrying industry, 30.00% in soil and stone mining, 20.67% in ship building, 18.52% in metal mining, and 17.63% in pottery.

"(3) As for the degree of silicosis, 385 patients (11.26%) were classified to the 1st degree, 74 (2.15%) to the 2nd, 52 (1.52%) to the 3rd, and 29 (0.85%) to the 4th. These morbidity rates in each degree were higher than respective rates of all Japan, and attention had been pointed especially to the fact that the difference of the morbidity rate between Kyoto and all Japan was remarkable in serious degrees of silicosis."

Lavenne, F., Brasseur, L., Oelbrandt, L. & Belayew, D. Volumes pulmonaires et volume expiratoire maximum par seconde des pneumoconiotiques encore au travail. **[Pulmonary Volumes and Forced Expiratory Volume per Second in Pneumoconiotic Subjects Still at Work]** *Rev. Inst. Hyg. des Mines.* Hasselt. 1961, v. 16, No. 1, 3–12, 4 figs. [29 refs.]

A review of the literature concerned with the influences of silicosis and coalminers' pneumoconiosis on lung volumes shows that the results differ greatly. Some authors find that a reduction in vital capacity takes place in the early stages of pneumoconiosis and that as the X-ray appearances become more marked the vital capacity diminishes proportionately. Other workers consider that micronodular pneumoconiosis does not affect the vital capacity, and no significant differences in any age-group were noted between Welsh coalminers suffering from extensive micronodular pneumoconiosis (category 3) and others radiologically normal.

The principal lack of agreement lies in the relationship between the radiological appearances of micronodular pneumoconiosis and the vital capacity values of FEV. The authors therefore felt that this problem should be investigated and they felt that the simplest method was to deal only with subjects still at work and thus to eliminate other factors such as bronchitis which are capable of affecting lung function tests. Two doctors in the coalmining industry were accordingly asked to send volunteers chosen at random from men still at work, aged 35 to 45 years of age, who had been exposed to a dust risk for at least 10 years. It was requested that the various different radiological appearances should be represented.

95 volunteers were examined of whom 78 were in the age-group indicated and 17 others who were just above or just below the age limits laid down. Details are given of the X-ray technique, and the classification used in interpreting the radiographs was that of the International Labour Office (Geneva, 1958). A table shows the distribution of radiological categories at each age from 35 to 42 years and it was noted that the X-ray appearances progressed to some extent with age. The apparatus and methods used in estimating the vital capacity and FEV are fully described and the results are given in a series of tables amplified by descriptive text. Predicted values for vital capacity, residual volume, and 1·0 second forced expiratory volume were calculated according to formulae worked out by research workers of the European Coal and Steel Community.

As a result of this study the following conclusions were drawn. Among miners about 40 years of age still at work and without respiratory discomfort there was a moderate but significant reduction of vital capacity which

fell to 85% of the predicted value. Since the reduced vital capacity was not accompanied by an increase of residual volume it must be directly related to the pneumoconiosis present. There was a slight reduction in the vital capacity between categories 1 and 2 but between categories 2 and 3 an abrupt effect showed itself. It is possible that if a greater number of subjects had been examined in categories O, Z, 1 and 2, changes as statistically significant as those noted between categories 1 and 2 might also have been found. Variations in FEV followed a similar pattern and the difference between categories 2 and 3 of simple pneumoconiosis was slightly significant. The fact that no confirmation of British work, indicating that the FEV was reduced solely as a result of employment as a miner, could be obtained was probably the result of a different method of selection of subjects. Reductions of the absolute value of FEV found among workmen still at work and of X-ray category 3 of the International Classification are to be attributed essentially to pneumoconiosis. Concomitant bronchial troubles play only a minor role.

These findings are of practical importance in Belgium since defective respiratory function attributable to pneumoconiosis forms one of the criteria on which a disability pension may be awarded. *G. F. Keatinge*

KREMER, R., MAJOIS, J., BAUDREZ, J. & LAVENNE, F. Étude du débit cardiaque et du volume sanguin central par radiocardiographie. Technique, corrélation avec la méthode de Fick, reproductibilité des mesures. [**Study of Cardiac Output and Central Blood Volume by Radiocardiography. Technique, Correlation with Fick's Method, Reproducibility of Measurements**] *Rev. Inst. Hyg. des Mines.* Hasselt. 1961, v. 16, No. 1, 13–20, 5 figs.

In order to measure the mean time of the pulmonary circulation, the cardiac output and the central blood volume, the principles of the Stewart-Hamilton method in which dyes were used has been applied to radioactive tracer substances in conjunction with radiocardiography. The term "central" blood volume is employed in this study in preference to pulmonary blood volume on the ground that it is a more exact description, since the mean pulmonary time includes the time taken for the stain to pass through the heart, and because the calculated blood volume includes the blood volume of the lungs and the blood volume of the heart, of which part is not capable of precise estimation.

The technique originally described consisted of injecting into a vein in the antecubital fossa a known quantity of serum albumin labelled with radioactive ^{131}I. Intracardiac curves were then recorded by a scintillometer placed in the praecordial area and connected with a rate meter. The first passage of the stain substance through the heart was recorded in the form of a curve with 2 summits and from it right and left tracings could be reconstructed by extrapolation. However the authors met with considerable difficulties in obtaining a diphasic curve in chronic lung conditions. Very often the right and left curves were joined together and it was impossible to calculate the mean time. This particular difficulty was attributed to positional abnormalities of the heart, as for example in emphysematous subjects who often show a small vertical heart rotated clockwise. Moreover slight displacement of the collimator can cause important alterations in the curves, and in addition there are considerable variations in the negative intrathoracic pressure in emphysematous people which reduce the chance of obtaining a biphasic tracing, because the time taken to pass from the antecubital vein to the right auricle is too great. As a result the original technique has been modified and the tracer substance is injected directly into the superior vena cava so that it reaches the heart without delay, and by this means excellent curves can be obtained which are easily reproducible whether at rest or on exertion. Exact details of the method are described. The total blood volume, the cardiac output and the "central" blood volume can be calculated from a knowledge of the final level of radioactivity, the final concentration of radioactive substance in the blood and the haematocrit.

37 subjects (normal people, patients suffering from lesions of the mitral or aortic valves, affections of the lungs and bronchi, and pneumoconiosis with and without cor pulmonale) have been investigated. In 21 cases tests were carried out entirely at rest and in 16 both at rest and on exertion. The results were compared with 54 cases in which the cardiac output was measured by Fick's method and the correlation between the two series was satisfactory (correlation coefficient 0·833). The "central" blood volume, measured in the manner described by the authors, averaged 1200 cc. in the normal man and was equal to 21 to 25% of the blood volume. These measurements again compare very satisfactorily with those published by LAMMERANT (*Le volume sanguin des poumons chez l'homme*, 1957, Bruxelles: Arscia). In 23 cases the reproducibility of the method was checked by measuring the "central" blood volume twice at rest, with an interval of 30 minutes between tests. The correlation was very good (correlation coefficient 0·897). Thus, despite large variations in the cardiac output and in the mean "central" circulation time, the "central" blood volume remained fairly constant. The method therefore seems suitable for the investigation of cardiac output and of "central" blood volume at rest and at exercise in pneumoconiotic and emphysematous patients and a study has been planned of which the results will be published later. *G. F. Keatinge*

MINETTE, A., VAN WYMEERSCH, L., GIELEN, E., DEGUELDRE, G. & BELAYEW, D. Étude expérimentale de la fonction respiratoire au cours d'efforts en présence de poussières de mines de charbon. Comparaison de la sensibilité bronchique aux poussières et à l'acétylcholine. [**Experimental Study on Lung Function during Exercise in the Presence of Dust from Coalmines. Comparison of the Sensitivity of the Bronchial Tree to Dusts and Acetylcholine**] *Rev. Inst. Hyg. des Mines.* Hasselt. 1961, v. 16, No. 1, 21–33, 3 figs. [13 refs.]

The effect of the dust in coalmines on the respiratory passages has been the subject of many investigations but

a review of recent literature shows that the findings of authors vary greatly, According to some, broncho-constriction appears after exposure to dust while others have not found any evidence that this is the case, and similar contradicatory results have been reported after the inhalation of dust produced in other industries. The authors have therefore undertaken a further study of the problem.

44 subjects participated, all volunteers and fully co-operative. 3 of them had never worked in a dusty atmosphere. 41 were miners used to coal-face work, and 33 of these men at recent examination had shown clear sensitivity to acetylcholine, in some cases accompanied by symptoms or auscultatory signs of bronchitis. The 8 other miners were not sensitive to acetylcholine, but did have symptoms or signs of bronchitis. The group was therefore a selected one and was not representative of the generality of miners.

All the subjects were exposed for one hour to a dusty atmosphere in a special dust chamber. The atmospheric conditions maintained in it, and the methods used to control them, are described. The dust used was coal with a low ash content (maximum 10%) and a silica content not exceeding 2%. The number of particles varied from 500 to 16,730 per cc. of air and their size ranged between 0·5μ and 5μ. Before going into the dust chamber each patient was subjected to a comprehensive clinical and radiological examination, determination of vital capacity, of forced expiratory volume, a series of scratch tests with the object of revealing any possible allergic susceptibility and an eosinophil count. Finally a study was made of lung function after effort: oxygen utilization and excretion of CO_2 were estimated, and the respiratory equivalent for oxygen and carbon dioxide and of the respiratory quotient after 10 minutes of moderate effort of 80 watts was also recorded. The apparatus and technique used are fully described. During the first 50 minutes of dusting the patients undertook 5 spells of exercise at 80 watts lasting 5 minutes, with a rest interval of the same duration. During the rest periods auscultation was carried out and the heart rate and the oxyhaemoglobin saturation estimated. For the whole of the last 10 minutes in the dust chamber the subjects exercised at 80 watts and in the last minute the ventilation, the oxygen utilization and the carbon dioxide excretion were again measured.

Immediately after the end of the exercise the vital capacity and FEV were estimated, followed by pharmacodynamic tests with acetylcholine and aluedrine according to a technique previously described by two of the authors [Minette and Van Wymeersch, this *Bulletin*, 1959, v. 34, 135]

The results are given in a series of tables with explanatory text but there was no significant change in the findings before and after exposure to dust. Analysis of individual cases showed that in 8 subjects the FEV decreased by at least 10% and increased by at least 10% in five others. Although similar variations in FEV may occur after exercise in non-dusty environments, the reduction in the 8 miners indicated was thought to be due to bronchospasm since they all belonged to the group of 33 patients sensitive to acetycholine and 7 of them also to the group of 21 complaining of dyspnoea in dusty environments. *G. F. Keatinge*

Gobbato, F., Zagarese, G., Alfieri, E., Berra, A. & Reggiani, A. Relazione tra dati spirometrici e reperti elettrocardiografici nell'insufficienza respiratoria da silicosi polmonare. [**Relation between Spirometric and Electrocardiographic Data in Respiratory Insufficiency caused by Pulmonary Silicosis**] *Med. d. Lavoro.* 1961, Mar., v. 52, No. 3, 167–84, 5 figs. [Numerous refs.] English summary.

Electrocardiography is still the simplest and quickest method of establishing the existence of cardiac complications in chronic lung conditions, since in routine clinical work the measurement of intracardiac pressure is not practicable. However, it is difficult to be certain at what stage of disease and at what degree of pulmonary insufficiency evidence of early signs indicative of cor pulmonale shows itself. This study is an attempt to examine the relationship between spirometer readings and electrocardiographic [ECG] findings in respiratory insufficiency in a selected sample of subjects with silicosis in an advanced stage of the disease. 100 subjects were chosen from the records of 1,000 people treated in recent years at the Occupational Health Institute in Padua, and in particular, patients whose FEV was 55% of normal or less. Estimation of respiratory function was carried out in the sitting position and the tests performed were vital capacity and FEV; from the results obtained on these tests the Tiffeneau index and indirect maximum ventilation were calculated. 12 tracings were taken with the electrocardiogram; standard leads, amplified unipolar limb leads and praecordial leads. The findings are discussed and analysed under the headings of atrial complexes, rapid ventricular complexes in peripheral leads, rapid complexes in praecordial leads, and final ventricular complexes.

In summary it was found that in 34 patients (34% of the observed) at least 5 ECG features were present usually considered as "indicative" and pathognomonic of cor pulmonale. The relationship between ECG findings and those obtained by spirometry was then examined and the patients were divided into 3 groups according to the degree of respiratory insufficiency noted, thus there were 44 subjects with FEV between 55% and 45% of normal, 33 whose FEV ranged from 44% to 30% of normal, and 23 with FEV below 30% of normal. It was found that the incidence of ECG signs consistent with the presence of cor pulmonale increased progressively from the first to the third group in direct relationship with the amount of respiratory insufficiency. When the vital capacity was less than 70% of normal and when the Tiffeneau index was less than 45% of normal, similar observations were made. The mean values of these three tests have been calculated, and expressing the vital capacity and FEV as percentages of normal the figures were: VC=62·7%, TI=45·1%, FEV=37·3%. Although these criteria may not be entirely valid from a strictly statistical point of view they are of undoubted practical use as an indication of the degree of functional disturbance which may be expected to be accompanied by an ECG picture pathognomonic of cor pulmonale. Nevertheless it is not impossible to encounter patients whose FEV is reduced to 50% of normal but in whom there is little or no change in the ECG tracing.

The results of this survey are compared with the findings of other authors and although no gross anomalies were noted nevertheless there were some differences which, however, are attributed to diverse criteria of the significance of ECG changes associated with chronic lung disease. The limitations of diagnosis based on ECG tracings alone are emphasized and McMichael (Daley *et al., Clinical Disorders of the Pulmonary Circulation*, 1960, London, Churchill) is quoted for the statement that up to 30% of elderly patients suffering from respiratory conditions may have a left ventricular lesion in addition to right ventricular hypertrophy. Finally there is a discussion on the possibility that reversible changes in the ECG may take place as a result of remissions of inflammatory lesions of the bronchi which can lead to alterations of alveolar ventilation, of interchanges of gases and of the blood supply in the pulmonary circulation. The authors intend to pursue this theme in another publication. *G. F. Keatinge*

Davies, C. N. **Size, Area, Volume and Weight of Dust Particles.** *Ann. Occup. Hyg.* London. 1961, June, v. 3, No. 4, 219–25. [16 refs.]

This is an important theoretical paper in which the author demonstrates the difficulties of comparing microscopic estimates of dust counts over limited size ranges with gravimetric estimates using size selectors based on settlement.

Reference is made to Cauchy's theorem which states that the total surface area of particles without re-entrant angles equals 4 times their total projected area if the particles are in random orientation. When particles of irregular shape settle in a sedimentation cell or are deposited on a thermal precipitator slide they are not in random orientation but will tend to have their largest diameter parallel to the plane of deposition rather than at right angles to it. Therefore projected diameter measurements will make such particles appear larger than if they were observed in motion.

In discussing volume shape factor, the author refers to large variations found by Robins (*Brit. J. Applied Physics*, 1954, Suppl. 3, p. S.82). Stokes diameters are discussed and attention is drawn to the fact that for any given Stokes diameter there is, for irregularly shaped particles, a wide range of projected diameters, caused by variations in shape, aggregation or density.

G. Nagelschmidt

MacEwen, J. D., Urban, E. C. J., Smith, R. G. & Vorwald, A. J. **A New Method for Massive Dust Exposures by Inhalation.** *Amer. Indust. Hyg. Ass. J.* 1961, Apr., v. 22, No. 2, 109–13, 6 figs. [10 refs.]

The method described uses a closed circuit in which the dust is mixed with air and led up to a circular inhalation chamber through a vertical cylinder in which the coarser dust falls out. The inhalation chamber has 6 ports round its circumference, through which the noses of the animals being exposed project. The design ensures that little of the body of the animal is exposed and animals up to the size of rats can be used. In tests the median diameter of particles generated was less than 3 microns, and the authors claim that the chamber concentrations are reproducible and that materials used can be recovered if necessary. *John McK. Ellison*

Collet, A., Voisin, G. A., Daniel-Moussard, H. & Toullet, F. **Production of Antibodies by Quartz and Beryllium Oxide.** *Arch. Environment. Health.* Chicago. 1961, Apr., v. 2, No. 4, 409–17, 5 graphs. [36 refs.]

"The authors used 3 groups of guinea pigs: a control group, a group given injections of quartz + homologous cells + homologous serum, and a group given injections of beryllium oxide + homologous cells + homologous serum, according to the usual method for maximal immunization. After a time lapse of 40 days, serum samples were obtained from all of the animals in order to test, by the extremely sensitive method of passive cutaneous anaphylaxis, for antibodies against quartz, beryllium oxide, a mixture of quartz + cells + serum, and a mixture of beryllium oxide + cells + serum. All of the animals were likewise tested for intradermal reactivity against the 6 following preparations: quartz, BeO, quartz + cells + serum, BeO + cells + serum, cells alone, serum alone.

"The results were as follows: 1. No antibodies were formed against any of the substances tested. 2. None of the treated animals showed hypersensitivity to quartz, BeO, or homologous serum. 3. A moderate hypersensitivity was produced in the animals of the 2 treated groups for homologous polynuclear leukocytes.

"The significance of the above facts was discussed, especially with respect to the pathogenesis of silicosis.

Addendum

"While this work was being printed, we read a paper by G. H. Curtis (*Arch. Dermat. & Syph.* 64: 470–482, 1951) [this *Bulletin*, 1952, v. 27, 262] reporting positive results on sensitization toward *soluble* beryllium compounds. The fact that we used an insoluble dust (BeO) might possibly explain the discrepancy between these results and ours."

Mosinger, M., Aynaud, R., Fiorentini, H., El Feki, M., Cartouzou, G., De Bisschop, G. & Bouisson, M. Sur le métabolisme de la silice. La silicémie et la siliçurie dans la silicose humaine et expérimentale. [**The Metabolism of Silica. Silica in the Blood Stream and in the Urine in Human and Experimental Silicosis**] Reprinted from *Rev. Lyonnaise de Méd.* 1959, Dec. 30, v. 8, No. 20, 1375–94.

The first part of this lengthy paper deals with the measurement of silica in the various organs, tissues and biological fluids. Techniques for estimating silica are reviewed and criticized. The methods for determining silica in the various organs and tissues, in the blood and in the urine, are all dealt with under separate headings and the authors' preferences are indicated. However, they

felt that a single method would be preferable and accordingly they adopted a technique based on their own experience and on the experimental work of RAMEL and other authors. It is nevertheless necessary to destroy organic material before silica can be estimated and for this reason they continued to use the method described by ISAACS for this purpose. Full details are given of the experimental procedure followed.

The second part of the paper is devoted to the metabolism of silica in silicotic subjects and it is pointed out that silica is an element which exists in every organ and tissue. Figures in terms of SiO_2 per litre in the blood, serum, erythrocyte and urine, published in 17 different papers from 1910 onwards, are given in the form of a table which indicates how findings have varied from author to author. The errors which may arise owing to the presence of iron and of phosphates are mentioned and attention is drawn to the importance of the former when estimations of silica in the blood are concerned and of the latter when it is the content in the urine which is in question. Determination by the authors in 6 normal people of silica in the blood varied between 9 and 17 mgm. per litre with a mean of 14 mgm., and in 5 normal people the amount of silica present in the urine gave a mean value of 21 mgm. per litre, the individual measurements varying from 11 to 29. Similar estimations were made in 9 miners and the results are given in a table; however, the figures, although variable, came quite close to those of normal persons. There was no relationship between the level of silica in the blood and in the urine [compare the experiment on dogs, below]: it is important to express values of silica in the urine both in mgm. per litre and in mgm. per 24 hours since the latter is very much more constant and a better indication of the excretion of this substance. Protein fractions, glucoproteins and lipoproteins in the serum were studied by paper electrophoresis and a table shows the results.

The third part of the paper is concerned with the metabolism of silica in normal and silicotic animals. Experiments were carried out on dogs, guineapigs and rats. Most of the work was done on dogs: an estimation was made of the silica content of various organs in 5 dogs chosen at random which had not been dusted and the results are set out in a table. It was found that the level of silica in the trachea, bronchial lymph nodes and in the lungs was high, which the authors attribute to the fact that since most dogs live in towns they are exposed to the same hazards of dust and fume as man. 2 dogs were given quartz intraperitoneally in the proportion of 5 gm. per kgm. (from 40 to 50 gm.) and 5 others received quartz by the bronchial route after tracheal intubation. Of the first 2 dogs one was killed 9 days after injection and the other died 52 days later.

The results are tabulated and in the case of the first dog the amount of silica present in the tracheo-bronchial, mesenteric and peri-pancreatic lymph nodes was greatly raised and to a lesser extent in the adrenals and right heart, whereas in the second animal, although the abdominal, mesenteric and peri-pancreatic lymph nodes contained considerable amounts of silica, they were notably less than those found in the dog killed 9 days after injection although in the liver, spleen and kidney, the levels were greater. The 5 dogs given quartz by the bronchial route all received 6·5 gm. to 12 gm. in 4–5 divided doses, over a period of about 2 months. 4 of them were killed soon after the last injection but the fifth was not killed until 3 months after the final administration of quartz. The 4 dogs which were killed promptly showed an increased amount of silica in the tracheo-bronchial and abdominal lymph nodes and raised quantities were also found in the lungs but not equally throughout the lobes, a phenomenon which is attributed to an unequal distribution of quartz at the moment of injection. In the 5th dog only normal levels of silica were found in the tracheo-bronchial lymph nodes but there was an increased amount in the peri-pancreatic lymph nodes. The right heart in all 5 dogs was rich in silica. The authors therefore consider that localization of silica takes place in the lungs and at the same time intense activity of the thoracic and abdominal lymphatic system occurs with absorption of much silica. This view is supported by the results obtained in the 2 dogs given quartz by the abdominal route and it is clear that whether administered intraperitoneally or intratracheally the silica remains to a great extent fixed at its site of entry. The right heart also plays an important part and the adrenals in the early stages after administration of quartz are particularly active. The highly vascular spleen rich in reticulo-endothelial tissue contained only a small amount of silica but when it was given intraperitoneally great quantities are present.

Blood samples were taken from all 5 dogs immediately before each injection of quartz was given and the results are indicated in a table which shows that during the 4 weeks which followed an injection the silica content fell in a very marked manner although 2 weeks later the level rose, approaching the normal amount. The whole process is undoubtedly complex and may be associated with the formation of a phospholipid silica compound.

The urine output of 3 dogs excreted during 3 days was examined systematically and the mean silica content was found to be 30 mgm. per litre. Studies made daily on the urine of a dog which had been given 20 gm. quartz in physiological saline by the intra-abdominal route revealed a number of interesting features, for example, a high *p*H was noted which may possibly be a necessary phenomenon to enable the organism to rid itself of silica. The urine was brownish-red in colour while silica was being excreted but became normal when elimination was complete. No adequate explanation is available to explain why this should be so. The urine was rich in minerals and carbonates, which may be related in some way to the metabolism of silica. Observations over 11 weeks showed that excretion of silica in the urine fell precisely in accordance with the level of silica in the blood stream.

Similar experiments were carried out on 8 guineapigs which were studied in order to establish the normal levels of silica in the various organs of these animals and experiments similar to those undertaken in the dogs were carried out on 26 other guineapigs with similar findings. The metabolism of silica was also studied in 7 rats again to establish normal levels in the various organs and tissues and in addition 6 animals were submitted to intraperitoneal injection of quartz on the basis of 4 gm. per kgm. or 8 gm. per kgm. in two divided doses. 3 rats were given intratracheal injections and in both

cases the results obtained were comparable with those which were recorded during the investigation of the dogs.

It is concluded that the study of the silica content of the blood and in the urine is a necessity in silicotic patients, as is the measurement of silica in the lungs and viscera in post-mortem material. Experimental work on the measurement of silica in the body fluids and viscera makes a contribution of much interest towards the understanding of the silicotic process and it is held that these studies have shown that the metabolism of silica takes place partly because the inhaled or injected silica goes into solution. *G. F. Keatinge*

Cruz, E., Schüler, P., Oyanguren, H., Salvestrini, H. & Del Solar, E. Silicomas grandes nódulos silicóticos que simulan tumor pulmonar. [**Silicomas: Large Silicotic Nodular Lesions simulating Carcinoma of the Lung**] *Rev. Med. Chile.* 1960, Nov., v. 88, No. 11, 875–82, 6 figs. [19 refs.] English summary.

In the majority of cases silicosis presents in the classical form with multiple fibrotic nodules at first separated from each other but later tending to coalesce. Sometimes, however, the picture is radiologically and pathologically atypical and the so-called silicoma appears as an isolated, relatively sharply defined, fibrotic mass with the histological characteristics of silicosis: radiologically a more or less rounded shadow is present with little or no characteristic disseminated micronodulation. In these cases therefore the differential diagnosis between bronchial carcinoma, tuberculosis, hydatid cyst, etc., is a serious problem. The history, clinical examination, and X-ray investigation do not usually succeed in elucidating the diagnosis and even when recourse is had to additional investigations such as bronchoscopy, sputum examination, biological tests, etc., doubt may remain. A high proportion of rounded pulmonary shadows are held by many authors to be malignant and figures are cited of an incidence varying from 36·7% to 49%. Thus precise diagnosis is of much importance and in many cases an exploratory thoracotomy is needed although even then the surgeon cannot always be sure whether the condition is benign or malignant. Reference to the literature shows that silicoma is seldom mentioned in the differential diagnosis of isolated pulmonary shadows.

In 6 years the authors have observed 4 cases in their own clinic, and they also report 2 others which were treated elsewhere. All 6 are described in detail and form the clinical material on which the present paper is based. The only common factor was the fact that the patients were all over 40 years of age and the development of silicosis could not be ascribed to any pre-existing pathological state. In only one could exposure to risk have been considered greater than average and in the others it was certainly low.

Although development of these masses can take place very rapidly—under a year in one patient—it is possible that they may remain unchanged for relatively long periods of time and may even diminish in size. It is emphasized that clinical, laboratory and radiological studies do not suffice for diagnosis. The one useful line to follow is to evaluate the previous occupational history: it is essential to make enquiry about the nature of every job the man has done throughout his working life and the length of time he has been engaged at each occupation. Above all the doctor should have a comprehensive knowledge of those tasks which in fact carry a risk of silicosis. But even a comprehensive work history may not enable the diagnosis of silicoma to be made with certainty and in the majority of cases it will be necessary to undertake an exploratory thoracotomy. At operation, if doubt remains about the nature of the mass, the surgeon should insist on immediate microscopy of biopsy material.

[A careful occupational history and a knowledge of work processes on the part of the doctor are indeed essential in assessing any case of pneumoconiosis. However, the fact that in 2 of the 6 cases described false positive results were reported on cytological examination of the sputum might give rise to unjustified lack of confidence in this test.] *G. F. Keatinge*

Milijic, B. & Miletic, Vida. A propos de deux cas d'apparition rapide de silicose. [**Two Cases of Rapidly Developing Silicosis**] *Med. d. Lavoro.* 1961, Mar., v. 52, No. 3, 161–6, 2 figs.

In the course of construction of a tunnel as part of a hydroelectric scheme in Macedonia, rapid development of silicosis took place in a number of workers who had been employed for 6 months to 2 years. Great quantities of dust were evolved in excavation across a rocky countryside and the workers were not provided with efficient personal protection, nor was there any attempt at suppression of dust. 7 cases have previously been reported by Petrov (*Zbornik radova* II *Kongresa leh, Srbije*, Nis, 1955, 386) and another by the present authors [this *Bulletin*, 1960, v. 35, 433]. All these were discovered by chance as a result of obligatory radiography of all industrial workers. 2 other cases are now described.

A man aged 30 years who had worked for 6 months in 1951 on the tunnel project was examined by X-ray in 1956 and was regarded as suffering from pulmonary tuberculosis. He was treated with streptomycin, PAS, and isoniazid, and spent several months in a sanatorium. For 2 years he was in and out of hospital, returning to work at intervals, and eventually his condition was diagnosed as silicosis. Apart from sweating at night at times the man had no complaint and although X-rays of chest showed appearances consistent with silicosis, clinical examination revealed little of note. Examination of sputum and other laboratory investigations also were negative save for a positive intradermal reaction after 48 hours but the vital capacity and the Tiffeneau index were only 83% and 88% respectively of the theoretical values. However, other lung function tests including maximum pulmonary ventilation, minute ventilation and oxygen absorption, were within normal limits or rather better. When the diagnosis was established the patient was discharged from hospital; he has been at work as a janitor and has been kept under surveillance at a clinic for occupational diseases. At his last examination in 1959 he claimed to be free of all discomfort.

The second case occurred in a man of 29 years who had not been employed in a dusty atmosphere until 1951, but from that year onwards until 1954 he worked a total

of 22 months at intervals in the construction of the tunnel. In July 1957 in the course of X-ray examination of workers lung changes were discovered which were held to be tuberculous and for 1 month he was treated with streptomycin, PAS and isoniazid. At the end of that time he was sent for further investigation to the Institute for Tuberculosis at Belgrade, and on questioning he said he was short of breath, lacked energy, and was troubled with a cough accompanied by a small amount of sputum. Examination showed a poorly developed subject, underweight and running a slightly raised temperature. On clinical examination prolonged expiration was noted and at the left base sibilant and creaking rales were present. X-ray of chest revealed numerous ill-defined small shadows. The hila were somewhat enlarged and the left ventricle was enlarged and hypertrophied. The electrocardiogram showed no pathological change. In this case also sputum tests and laboratory examinations were negative except that the intradermal reaction was positive after 48 hours. Vital capacity and the Tiffeneau index were 67% and 45% respectively of the theoretical values, but the other lung function tests as in the previous case were within normal limits. During his stay in hospital anti-tuberculous treatment was given but the condition did not improve and he was put on pension and is kept under regular surveillance. Since his discharge the condition is unchanged and the man is still short of breath. The last chest X-ray showed a slight degree of extension of the silicotic appearances.

The authors think that the explanation of rapid development of silicosis, which has not, however, progressed or led to a fatal outcome, is to be found either in the great quantities of siliceous dust which the subjects have inhaled or because they are unduly susceptible. The work was carried out without water suppression and great clouds of dust were present but unfortunately it was not possible to check the chemical composition, particle sizes, or concentration. Susceptibility to silicosis is attributed partly to an inability of the subject to eliminate noxious substances, but also to an immunological state specific to the condition and reference is made to the work of VIGLIANI and that of GRIECO [*ibid.*, 1958, v. 33, 760]. Cases such as these underline the importance of periodical examinations and of the need to safeguard the worker both by engineering techniques and measures of personal protection. *G. F. Keatinge*

CHATGIDAKIS, C. B. & THERON, C. P. **Rheumatoid Pneumoconiosis (Caplan's Syndrome). A Discussion of the Disease and a Report of a Case in a European Witwatersrand Gold Miner.** *Arch. Environment. Health.* Chicago. 1961, Apr., v. 2, No. 4, 397–408, 9 figs. [23 refs.]

The Johannesburg Pneumoconiosis Research Unit has performed 576 autopsies on European gold-miners in the last 4 years, and 11 cases of rheumatoid disease have been found, giving an autopsy incidence of 2%. Only one of these (case 1) showed an active inflammatory reaction in the rheumatoid pneumoconiotic nodules. There were 3 probable cases of burnt-out, inactive rheumatoid pneumoconiosis, one other patient showed silicotic islets and a typical subpleural rheumatoid nodule in the lungs, and the remaining patients showed no evidence of rheumatoid pneumoconiosis.

The description of case 1 is detailed and accompanied by several excellent illustrations. It related to a man aged 63 years at death who had spent 8 years underground from 1937 to 1945. Since 1945 he had suffered from joint pains and since 1947 from chest symptoms. X-ray examination of the chest in 1954 showed numerous small ill-defined opacities about 5 mm. in diameter in both upper lobes, and this appearance did not change much up to the time of death. Histological examination showed 3 types of lesions in the lungs—nodules resembling tuberculo-silicotic nodules but which were probably burnt-out nodules of rheumatoid pneumoconiosis, larger nodules composed of aggregations of smaller nodules but with peripheral active inflammation and showing a slight degree of palisading, and nodules smaller than typical silicotic nodules showing non-specific fibrosis. In the necrotic centres of some of the larger nodules there was elastic tissue arranged as in the alveolar walls. No evidence of tuberculosis was found during life or in the tissues after death.

Not all cases of rheumatoid disease with exposure to dust develop rheumatoid pneumoconiosis so that some third factor must be necessary. This may be tuberculosis in some cases; in others it may be some other lung infection. *A. T. Doig*

MAROC MÉD. 1961, May, v. 40, No. 432, 429–91, 21 figs. [Numerous refs.] Les pneumoconioses. [**The Pneumoconioses**].

This series of 10 papers covers some subjects directly concerning the work of the industrial doctors in Morocco but some papers are of more general interest. The first, on *Retentissement cardio-vasculaire des pneumoconioses* by P. SADOUL, J. METZ, F. CHERRIER and F. R. PARMENTIER (pp. 429–436), is concerned particularly with the role played by micronodular (or nodular) pneumoconiosis in producing pulmonary arterial hypertension. 46 pneumoconiotic patients voluntarily submitted themselves to intensive investigations including cardiac catheterization, as well as spirometric and clinical tests. The respiratory exchanges were studied with the aid of the Fleisch metabograph [SCHERRER, this *Bulletin*, 1959, v. 34, 1135]. The various methods used in the investigation are described. The results obtained centred round the relation between the mean pulmonary arterial pressure and (1) the X-ray category of the abnormality; (2) the ratio of the maximal voluntary expiration per second (VEMS) to vital capacity; (3) the oxygen saturation of the blood. The first of these results is the most interesting. 17 of the 29 patients showing simple pneumoconiosis on X-ray examination had hypertension (59%) and 7 of the 17 with masses (41%). The patients with simple pneumoconiosis were not necessarily suffering from emphysema.

According to the authors, the presence of a moderate hypertension, raised distinctly by exercise is an indication for stopping manual work. The assessment of disablement for compensation has already been discussed by SADOUL and METZ [*ibid.*, 1959, v. 34, 1261].

Two papers deal with atypical silicosis. *Silicoses atypiques à forme ganglio-pulmonaire*, by J. J. JARRY,

E. Balgairies, P. L. Masure and L. Lenoir (pp. 437–441) is a description of a type of patient with a radiological shadow at the hilus which suggests at once carcinoma of the lungs. The condition has been described several times and Kergin [*ibid.*, 1953, v. 28 718] is particularly quoted. The case described by the authors was of a coal-miner age 38, who was admitted to hospital in 1957 with a suspected carcinoma of the lung. His X-ray picture then showed a triangular shadow at the right hilus with a background of micronodular shadows. He was submitted to a series of thorough investigations and in spite of negative smear and culture tests was submitted to a course of antituberculous antibiotic treatment but there was no X-ray change. Carcinoma was eliminated because of the duration of the shadow: a study of a film taken in 1950 showed an enlarged right hilar gland. An exploratory thoracotomy was performed in 1959. An extensive fibrotic mass was found round the hilum and this histologically was composed of anthracotic fibrohyaline tissue. The differential diagnosis is fully discussed, since with a mass at the hilum, operation should be avoided in such cases. Repeated tests for the tubercle bacillus, bronchoscopic and bronchographic examinations, and examinations of previous films should be carried out before a biopsy or an exploratory thoracotomy.

The second paper on atypical silicosis, *Que penser de l'atypie dans la silicose* by M. LeHir, A. J. Guerrero, J. Variot and J. Bellanger (pp. 455–461) follows the same lines as a previous paper [*ibid.*, 1961, v. 36, 329].

F. Tolot discusses *L'évolution des images denses et des masses pseudo-tumorales de la silicose* (pp. 442–447), and gives the results of the study of the dossiers of 200 patients with such conditions. These masses may be considered as arising as a result of silicosis apart from any superadded infection. The immunity theory of silicosis rests on the responsibility of silicosis alone for this progression. The idea however that infection, particularly tuberculous infection, plays a part in producing these masses is widespread. The conclusion drawn by the author is that although the matter is not decided, it is certain that there is frequently an "entanglement" of silica and the tubercle bacilli. This should lead one to adopt a more dynamic attitude to these lesions. The question of the prophylactic inoculation with BCG is considered as well as that of chemotherapy. The latter should be undertaken at the time when the nodulation stage is passing into the stage of massive fibrosis.

Enquêtes itératives sur la silicose au travail de fond, by M. LeHir and A. Guerrero (pp. 448–454), gives a comparison of the results of examinations at Jerrada mine during 1956, 1957, 1958 and 1959. The first examination results are given in a paper by LeHir *et al.* [*ibid.*, 1959, v. 34, 1131]. The incidence of tuberculosis declined from 4% regularly each year to 1·5% in 1959. The patients with simple silicosis were considered in two groups, those with exposure of less than 10 years and those with over 10 years' exposure before the appearance of the silicosis. Followed through the years, the first group showed a greater tendency to progression than the latter, the risk being about 30% in the first group and 20% in the second. The first group should not continue to work underground, the second may be allowed to do so, under supervision

La silicose existe-t-elle dans les mines de phosphates de l'O.C.P., by J. Bendelac and Ch. Blaise (pp. 461–463). Phosphate is recovered from underground workings from seams of limestone; it is brought to the surface by conveyor belts. Drillers may be exposed to dust composed of particles less than 5 μ in size. The silica content of the dust was not ascertained but silica is rare in these mines. The amount of dust in some badly ventilated places was thought to mean a risk of pneumoconiosis. It was suggested that rubber dust from the conveyor belts might be dangerous but a report in 1953 from the Michelin factory proved that rubber particles were seldom under 15 μ in size. From the medical aspect, clinical and radiological examinations in 1957, 1959 and 1960 failed to reveal any cases of pneumoconiosis arising from work in these mines. It is concluded that the pneumoconiosis problem does not arise.

Utilisation du cytochrome C dans la dyspnée des silicotiques en clientèle et en milieu hospitalier, by D. F. Raguet (pp. 464–477). Cytochrome C has been used to lessen the dyspnoea of patients with cancer: its therapeutic action is to lower the demand for oxygen of the cells and so of the organism. 32 patients with silicosis were treated with the drug: 10 were volunteers treated specially, 9 in general practice and 13 in hospital. In 4 there was no change, in 23 the result was excellent and in 5 the result was doubtful. The injection is best given slowly intravenously of 60 mgm. in 20 cc. of the solvent daily. The good effect lasts for 3 months in some cases, but the long-term effect cannot be foreseen.

La législation sur la silicose au Maroc, by M. LeHir and J. Ritter (pp. 478–486). Silicosis has a legal definition in a decree of May 31, 1943: "Silicosis is a pulmonary fibrosis resulting from the inhalation of dusts containing free silica when there are radiographic signs accompanied by symptoms (dyspnoea and frequent bronchitis and cough) confirmed by functional tests of the respiratory system" [abstracter's translation]. A detailed description is given of the procedure for obtaining compensation and of the rules for change of occupation. As far as possible the silicotic miner carries on work either at his own trade or in a non-silicogenic occupation.

Médecine du travail et tuberculose pulmonaire à l'hôpital de l'O.C.P. à Khouribga, by J. Bendelac, Ch. Blaise and M. Nougarede (pp. 487–489). This paper dwells on the close collaboration of those in Morocco engaged in the campaign against tuberculosis and those engaged in industrial medicine, in preserving the health of the worker. The examinations carried out by the tuberculosis service yearly from 1957 to 1960 showed a steady reduction in cases of active tuberculosis discovered. Treatment is assisted by the prolonged sickness leave granted to the tuberculous worker. When the disease is healed or is quiescent suitable sheltered work is arranged. Among the suggestions for improving conditions it is suggested that the prolonged period of inactivity during treatment might be utilized by giving some form of training or education.

Dépistage radiologique systématique sur les lieux du travail au moyen d'une remorque itinérante, by J. C. Gregoire (pp. 490–491). This is a description of the X-ray plant carried on a trailer.

Charles L. Sutherland

GAMBINI, G. Analisi elettroforetica, immunoconglutinine ed agglutinine fredde antizymosan del siero degli asbestosici. **[Electrophoretic Analysis, Immunoconglutinins and Cold Zymosan Agglutinins in the Serum in Asbestosis]** *Med. d. Lavoro.* 1961, Mar., v. 52, No. 3, 185–90. [13 refs.] English summary.

In view of the immunological reactions reported by VIGLIANI, PERNIS, *et al.* (*Proceedings of the Congress of the Italian National Society for Occupational Health, Rimini*, 1959, in the press) in silicotic patients the present research was undertaken in order to find out whether the serum in patients suffering from asbestosis showed changes of a similar kind to those seen in subjects with silicosis. In 27 out of 29 patients definitely affected with asbestosis and treated at the Clinica del Lavoro in Milan it was possible to study the serum-protein picture, in 18 the immunoconglutinin was determined and the cold zymosan agglutinins were estimated in 19. In 19 cases asbestosis was uncomplicated by any other condition and this group was classified in 3 subdivisions according to whether the disease was held to be slight, moderate or advanced. The remaining cases included 6 complicated by tuberculosis either active or quiescent, in one patient asbestosis was associated with bronchial neoplasm, and in another chronic hepatitis was present. 10 normal individuals constituted a control group. As the numbers were small the study was limited to the 2 groups of patients with uncomplicated asbestosis and those in whom tuberculosis was also present, and in a table the results are analysed statistically.

Low levels of total proteins and albumin together with an increase of alpha 1 globulins were noted in all the subjects examined and only in very advanced cases of asbestosis was an increase of alpha 2 globulins and of gamma globulins found, usually when tuberculosis was a complication. On the other hand in silicosis the total serum proteins remain within normal limits throughout the course of the disease while gamma globulins are increased even in its early stages, and other serum globulins are only slightly increased in the terminal phase. There was an increase of immunoconglutinins in about 16% of cases of asbestosis and this finding is probably explained by antigen-antibody reactions brought about by superadded infection. The occurrence of cold zymosan agglutinins in about 30% of cases supports this hypothesis and to quote the authors " . . . we are very far from the 90% of positive cases met with in silicotics " [abstracter's translation]. In silicosis the presence of the immunoconglutinins is a concomitant of the pathogenic processes in the disease and as a result they are found in abnormal titres in almost all cases while in asbestosis they represent later superadded infection.

The results of this investigation have a clinical interest because they show once again that any analogies there may be between asbestosis and silicosis are quite superficial in character. *G. F. Keatinge*

WILLIS, J. B. **Determination of Lead in Urine by Atomic Absorption Spectroscopy.** [Correspondence.] *Nature.* 1961, July 22, v. 191, 381–2.

This method is particularly well suited for measuring traces of Pb. Blank values are negligible, there is no interference from other metals, and after chelation therapy inaccuracies possible with precipitation methods are avoided.

Good recoveries are shown when Pb, ranging from 0·01 to 0·05 p.p.m., was added to normal urine specimens or to similar specimens to which 15 μgm. Pb were added to serve as standards. Equivalent results were shown when pathological specimens were tested also by the dithizone method. The Pb is extracted from 50 ml. urine, of *p*H less than 4·5, by shaking with 0·5 ml. of 4% ammonium pyrrolidine dithiocarbamate and 1·5 ml. methyl *n*-amyl ketone. After standing, most of the lower layer is discarded. After centrifuging for 5 minutes the upper layer is removed by pipette. The remainder is stirred, centrifuged again and the upper layer is added to the first. This solution is sprayed into the 10-cm. air-coal-gas flame of the atomic absorption spectrophotometer. The absorption of the lead line at 2833 Å is measured and the instrument is calibrated by extracting and measuring a similar quantity of urine to which a known amount of Pb has been added.

The method is applicable to other heavy metals, and with Zn and Cd extraction is not necessary.

M. Patricia Fitzsimons

BELKNAP, E. L. **Modern Trends in the Treatment of Lead Poisoning. A Review of the Literature on the use of Edathamil Calcium-Disodium.** *J. Occup. Med.* Chicago. 1961, Aug., v. 3, No. 8, 380–91. [25 refs.]

LAMY, P., SENAULT, R., SADOUL, P., HUTTIN, R. & GUILLERM, J. Les opacités massives chez les mineurs de fer. **[Massive Pulmonary Opacities in Iron Miners]** Reprinted from *J. Français Méd. et Chirurg. Thoraciques.* 1959, v. 13, No. 3, 283–92, 11 figs.

The massive pulmonary opacities occurring in miners of iron ore who have not been exposed to other risk of pneumoconiosis are quite different from those which are caused by silicosis, since the latter are composed of fibro-hyaline tissue poor in cellular content and containing irregularly distributed dust particles while the former consist simply of masses of iron oxide. Moreover the lungs of iron-stone miners have a silica content hardly greater than normal and far below that found in silicotic lungs. The iron ore in Lorraine lies in limestone measures in which there is only 10% of silica and that in the combined form.

The present study is based on 45 original observations among miners who had never undertaken any other kind of work or had not been exposed to a risk of pneumoconiosis lasting more than one year. In 25 men the duration of exposure to risk had been for a period of more than 25 years and only in 4 cases had the exposure been less than 15 years. In none of these 4 men were the lesions characteristic and 2 of them later developed tuberculosis with positive sputum; it is considered probable that the X-ray appearances were not due to siderosis but were the results of tuberculosis superimposed on simple pneumoconiosis. In almost all the cases the X-ray pattern was definite and very suggestive

of pneumoconiosis with pinhead or micronodular shadows corresponding with Categories 2 or 3 ("p" or "m") of the Cardiff-Douai Classification. However, on 3 occasions, although characteristic pseudotumoral lesions were present, the lung fields showed nothing more than a reticular appearance. The possibility that massive opacities may occur in lung fields otherwise radiologically unremarkable must be underlined and proof that this can happen was obtained when pathological investigation performed after a lobectomy undertaken for a supposed neoplasm showed that the mass was in fact merely a large collection of oxide of iron. Radiologically the shadow is usually rounded or oval, although sometimes there is a collection of several masses with irregular outlines which may contain small calcified areas, but atypical forms are found and emphysematous bullae are often present. The masses vary in size, most of them on the Cardiff-Douai classification are of Type A although Types B and C are not rare; however, measurements at the greatest width of the masses showed that 5 were more than 6 cm., 18 from 3 to 6 cm., and 22 below 3 cm. in width. These massive opacities are nearly always situated at the apex: they were bilateral in 20 out of the 45 cases investigated and when present in both lungs the masses were usually about the same size.

Progression is limited and patients followed-up for more than 4 years have shown little change in the state of their lungs: in one case, after 6 years during which the condition was apparently stationary, tuberculosis developed with necrosis of the massive opacity, but apart from this instance to the authors' knowledge tuberculosis was present only in the 2 other cases to which reference has already been made. Absolute certainty on this point is lacking since the follow-up was not complete. Still there is no doubt that the outlook is on the whole more favourable than in pseudotumoral masses due to silicosis, particularly from the point of view of lung function.

As to the frequency of the condition: among 15,277 ironstone miners submitted to radiography of the chest with 10 cm. × 10 cm. film, 494 (3·23%) showed changes due to pneumoconiosis; and of these 494 films, massive opacities were present in 8 cases (1·6%). In another survey of 550 men, all employed at one mine, 28 were certified as suffering from occupational disease (of the lungs) and among them there were 2 cases in which pseudotumoral masses were present. Both these men had worked all their lives in iron mines and exposure to risk exceeded 30 years in each case. Retired miners were not included in this survey and it is probable that other cases of massive opacities would have been brought to light had they also been examined by X-ray. In still another investigation of 932 miners who were examined in consultation, 605 showed changes due to pneumoconiosis with massive opacities in 45 (7·4%). The authors think that the true incidence lies somewhere between the lower figure of 1·6% and the upper figure of 7·4%. Diagnosis is all-important and it is difficult sometimes to differentiate between a massive opacity and a carcinoma.

[Geologically, conditions do not differ much between the iron-stone mines in Lorraine and those in Cumberland, and British observers would not agree with some of the views expressed in this paper. Thus Craw (this *Bulletin*, 1947, v. 22, 571) has specifically stated that "The pathological anatomy of conglomerate fibrosis" (in haematite miners) "is similar to the massive fibrosis seen in all silicosis due to mixed dusts".] *G. F. Keatinge*

Schüler, P., Maturana, V., Cruz, E., Guijón, C., Vásquez, A., Valenzuela, A. & Silva, R. Siderosis pulmonar de los soldadores al arco. [**Siderosis of the Lungs in Electric Arc Welders**] *Rev. Med. Chile*. 1960, Dec., v. 88, No. 12, 957–62, 6 figs. [18 refs.] English summary.

A short account is given of the process of arc welding, and the siderosis which occurs in those engaged on it is briefly described. 210 arc welders employed in various organizations in Santiago, Chile, were submitted to a comprehensive medical examination including physical examination, lung function tests, determination of iron in the serum, and radiography of chest. A full anamnesis and occupational history were also obtained. Care having been taken to exclude from the study all those who had been at any time exposed to a risk of silicosis, 32 men remained in whom the radiological appearances showed the presence of pulmonary siderosis.

The X-ray picture is difficult to interpret and it is held that to a varying extent changes occur similar to those found both in silicosis and in asbestosis. In the cases most like silicosis nodules predominate and in those resembling asbestosis increased linear markings are noted at the bases, there is a generally reticulated appearance and blurring of the cardiac outline is present. In the majority of films the radiological appearances are suggestive of both affections. The similarity with asbestosis has been interpreted as due to the asbestos covering of some electrodes but it is pointed out that although in several cases observed in this study this appearance was seen, none of the welding rods used by these workers in fact had any asbestos covering. Some authors hold that the presence of nodulation is not necessary to a diagnosis of siderosis [this *Bulletin*, 1946, v. 21, 746]; nevertheless the criterion adopted in this study has been the existence of nodules in both lung fields coupled with characteristic reticulation. Hilar enlargement was present in 81% of cases, a "ground glass" appearance was noted in 46%, increased linear markings at the bases in 43%, and blurring of the cardiac outline in 31% of films examined. Radiological signs of emphysema have not been observed nor has any tendency to coalescence been seen. Although radiological improvement has been reported in retired welders, this has not been observed by the authors.

A straight X-ray examination of the abdomen was carried out in most of the workers to locate iron which might have been deposited in the liver or spleen. Unfortunately most of the films taken were technically unsatisfactory but in those in which it was possible to form an opinion, no changes were seen to suggest an accumulation of iron. Pulmonary function tests carried out in 24 subjects were practically all within normal limits. Haemoglobin and serum iron estimations were undertaken in 23 patients with pulmonary siderosis and in 18 normal subjects, to determine whether any changes in iron metabolism were brought about by its inhalation. There was a significant difference between the figures

obtained in the two groups since the patients with pulmonary siderosis showed a mean value for serum iron of 97·1 mgm. per 100 ml. compared with that of 119·7 mgm. per 100 ml. among the normal subjects. Further investigations into the iron metabolism of these patients are being carried out and the results will be published later. In no case was the haemoglobin level below 12·59%.

Only one reference has been found in the literature to necropsy material [*ibid.*, 1938, v. 13, 779] but among the workers studied there was a case of hydatid cyst and in the course of operation for this condition the opportunity was taken of noting the state of the lungs; the macroscopic appearance was quite normal save for the presence of considerable areas of brownish-red pigmentation variable in size but without emphysema or fibrotic reaction. The lymph nodes were not enlarged. A biopsy of lung was done and on microscopic examination phagocytosis of a brown pigment which gave the specific reactions for iron was observed. The majority of the phagocytes had accumulated in the alveolar lumen but they were also found in the alveolar walls and around the blood vessels and lymphatic channels. Infiltration by leucocytes was also present to a limited extent but there was no proliferation of histiocytes or fibroblasts. There were no signs of emphysema or vascular engorgement. The vessels included in the section were normal in appearance.

Among the 32 patients examined no respiratory complications were noted except in one patient in whom radiological signs of inactive tuberculosis were found.

The importance of a correct diagnosis in pulmonary siderosis is emphasized. Frequent diagnostic mistakes will only be avoided when the clinical picture of this pulmonary condition is generally known, when complete occupational histories are obtained, and a good radiological technique is followed.

[An interesting paper. The authors have broken new ground in trying to determine whether an accumulation of iron occurs in the liver and spleen in pulmonary siderosis and to assess the blood changes in this condition. The dearth of post-mortem material makes of particular value the report on the appearances of the lungs seen on thoracotomy and the results on microscopy of lung tissue obtained at biopsy.] *G. F. Keatinge*

JACOBS, M. B., GOLDWATER, L. J. & GILBERT, H. **Ultramicrodetermination of Mercury in Blood.** *Amer. Indust. Hyg. Ass. J.* 1961, Aug., v. 22, No. 4, 276–9, 1 fig.

DUBOIS, L. & MONKMAN, J. L. **Determination of Arsenic in Air and Biological Materials.** *Amer. Indust. Hyg. Ass. J.* 1961, Aug., v. 22, No. 4, 292–5, 1 fig.

HISER, R. A., DONALDSON, H. M. & SCHWENZFEIER, C. W. **A Rapid Analytical Method for the Determination of Beryllium in Air Samples.** *Amer. Indust. Hyg. Ass. J.* 1961, Aug., v. 22, No. 4, 280–85, 2 figs.

AMERICAN CONFERENCE GOVT. INDUST. HYGIENISTS. **Threshold Limit Values for 1961.** Adopted at the 23rd Annual Meeting, Detroit, Michigan, April 9–12, 1961. *Amer. Indust. Hyg. Ass. J.* 1961, Aug., v. 22, No. 4, 325–8.

[See also *Arch. Environment. Health.* Chicago. 1961, v. 3, 489.]

CERWENKA, E. A., Jr. & COOPER, W. C. **Toxicology of Selenium and Tellurium and their Compounds.** *Arch. Environment. Health.* Chicago. 1961, Aug., v. 3, No. 2, 189–200. [67 refs.]

This review surveys retention, excretion and toxicity of Te after dealing with Se about which more is known. On the whole Te and its compounds are less toxic, except tellurites. Sodium tellurite is more toxic even than the selenite, itself more toxic than the arsenite. The MAC for Te is 0·01–0·1 mgm. per $m.^3$ air. Hydrogen telluride is possibly the most toxic Te compound. It, though less easily accidentally formed, produces symptoms like those from hydrogen selenide; this irritant, toxic gas has a threshold limit value of 0·2 mgm. Se per $m.^3$, or 0·05 p.p.m. Se.

Water-soluble compounds can be absorbed through the skin. In the body they are reduced to dimethyl selenide or telluride—which cause the garlic breath—and to the elements. Tellurium breath lasts longer, is a variable early indication of absorption and can be temporarily decreased by ascorbic acid. However, this—and also BAL—increases toxicity from Te dioxide in animals. Excretion of Te is slow. The largest amount after injection is in the kidney, with little in the liver. Cumulation is a possibility. With Se compounds excretion holds pace, after saturation, with intake.

In prolonged experimental poisoning Se is distributed in liver, kidney, spleen, pancreas, heart and lungs. Liver degeneration is generally reversible but may end in cirrhosis. The spleen enlarges, anaemia develops, gastrointestinal bleeding occurs and the kidney shows mild tubular damage. In man chronic intoxication causes pallor, nervousness, depression, languor, gastrointestinal upset, odour of breath and sweat and occasional dermatitis.

Elemental Se has a relatively low toxicity but inhalation of dust or fume causes respiratory irritation. Se dioxide, selenious acid and its salts are among the more toxic and irritating compounds, causing dermatitis and burns. Na thiosulphate lotion or cream reduces the salt to the element and eases pain, especially under the nail. Se oxychloride is a liquid vesicant; after skin application it has been found in the liver and the rabbits died within 24 hours. Organic compounds are retained longer and vary in toxicity. The toxicity of plants growing in seleniferous areas is probably due to selenium-containing protein. A high protein diet may protect against Se intoxication.

Acute experimental poisoning with Te compounds causes restlessness, paralysis, convulsions, somnolence, unconsciousness and cessation of respiration. Men working with Te have complained of somnolence as well as odour of breath and sweat. Elemental Te is the least

toxic form. Care is needed where Te and compounds are used and also investigation into chronic toxicity.

M. Patricia Fitzsimons

BROWNING, E. **The Metabolic Significance of some Toxic Solvents.** *Ann. Occup. Hyg.* London. 1961, June, v. 3, No. 4, 231–46. [Numerous refs.]

This survey, packed with biochemical data, deals mainly with the influence of foreign substances and their metabolites on body enzyme systems and detoxication processes. It shows how compounds belonging to the same chemical group may differ in effects, *e.g.*, benzene, toluene and xylene. The general detoxication mechanism is first discussed and also certain enzymes. The solvents chosen are the more important and better known ones used in industry, and a few newer ones in which metabolic transformations have been studied among the aromatic hydrocarbons, chlorobenzenes, halogenated hydrocarbons, alcohols, chlorinated alcohols, glycols and carbon disulphide.

The relative non-toxicity of the alkyl benzenes (phenyl alkanes) apart from their irritant effect is related to the small amounts which are metabolized. Carbon tetrachloride is believed to cause liver necrosis by disruption of mitochondria; inhibition of oxidative phosphorylation occurs and liver cells release into the blood increased glutamic oxalacetic transaminase. This is not increased by trichlorethylene and of its many metabolites trichloroethanol excretion is a better criterion of exposure than tetrachloracetic acid. The ocular injury caused by methyl alcohol is probably due to a primary inhibition of retinal glycolysis by metabolites. Renal injury characteristic of the glycols is related to metabolism into oxalic acid. With carbon disulphide the mechanism is not understood but several enzymatic reactions are discussed: binding of peptides, proteins and amino-acids and production of dithiocarbamates which can be decomposed by the desulphydrase system; decrease in alkaline phosphatase activity which normally requires zinc and magnesium ions; excretion of them is increased (cholesterinaemia is involved with enzyme systems and metal complexes required as activators); copper, normally present in brain and spinal cord as part of cytochrome oxidase and co-factor A, is bound to the thiocarbamate groups and is decreased in pathological lesions of the nervous system. *M. Patricia Fitzsimons*

TACHIIRI, H., MATSUDA, H., ISHIHARA, A. & HAMASAKI, Y. **Roentgenologic Studies on the Chests of Occupational Gas Inhalers with special reference to Inhalation of Benzene.** *Med. J. Osaka Univ.* 1958, Dec., v. 9, Nos. 3/4, 511–16, 3 figs.

"1. Chest radiographs of 366 occupational inhalers of gases including benzene, chlorine, sulphurous acid etc. and 181 controls were obtained by direct roentgenography. They are differentiated into several divisions of definite categories by X-ray appearances of the chest and statistical comparisons were carried out as to frequency of exaggerated pulmonary markings and of some other abnormality of the chest.

"2. Benzene inhalers show exceptionally high value of frequency of exaggerated pulmonary markings in comparison to that of other gas inhalers or of control.

"3. Frequency of exaggerated pulmonary markings in control is remarkably small before 50 years of age, and it suddenly gets to 50% when they are over 50 years of age. On the other hand, percentage value of exaggerated pulmonary marking of benzene inhalers is generally larger than usual in comparison with not only control, but also inhalers of various gases. Elevation of percentage value of exaggerated pulmonary markings in benzene-inhalers seems to appear at a younger age than usual.

"4. If the period of gas-inhalation is within 2 years, there is no marked difference on frequency of exaggerated pulmonary markings between benzene- and various gas inhalers, but the differences between them become remarkable when the period of inhalation is over 2 years."

TACHIIRI, H., MATSUDA, H., HAMASAKI, Y. & ISHIHARA, A. **Roentgenologic Studies on the Chests of Occupational Gas Inhalers with special reference to Inhalation of Benzene. II.** *Med. J. Osaka Univ.* 1960, Dec., v. 11, No. 3, 293–301, 6 figs.

A previous mass X-ray survey had shown exaggeration and abnormalities of lung markings among 163 labourers in large factories where environmental conditions were good and where the permissible limit of 100 p.p.m. benzene was not exceeded. The incidence of such changes was 23·3%, and among 181 controls 12·2%. This survey includes small factories where concentrations of benzene were 100–400 p.p.m. The incidence was 33·3% among 72 labourers. In a bicycle plating factory, the incidence among 52 platers exposed mainly to sulphuric acid vapour was 15·4% and among 72 polishers exposed mainly to dust 13·9% In addition, the incidence of non-tuberculous and non-metastatic nodulation among these 3 groups was respectively 9·7%, 17·3% and 33·3%. Both sets of changes taken together were more frequent among the 72 high-benzene than amoung the 163 low-benzene subjects for each age-group and exposure period, the latter 1–7 years.

No radiological changes were seen in the lungs of rabbits exposed to 1,000 p.p.m. benzene for a few hours daily for 22 and 110 days. The lungs showed papillary proliferation of bronchiolar mucosa, peribronchiolar congestion and emphysema. *M. Patricia Fitzsimons*

BANNOVA, N. V. **[The Toxicology of Trichloroethylene]** *Gigiena Truda i Professional'nye Zabolevaniya.* Moscow. 1961, v. 5, No. 3, 9–14, 4 figs. [In Russian.] English summary.

[The American Conference of Governmental Industrial Hygienists recommends a threshold limit value for trichloroethylene of 200 p.p.m. of 1,050 mgm. per cubic metre. GRANDJEAN *et al.* [this *Bulletin*, 1955, v. 30, 785] suggested a level of 40 p.p.m. and quoted the value in the U.S.S.R. as 9 p.p.m. This article suggested a reduction of the latter recommendation.]

The work was carried out in 2 phases; experimental, in which was studied the effects on conditioned reflexes and the electroencephalograms of rats and the histology of the cerebral cortex, at the same time the products of metabolism in the urine were determined. Following this, investigations were carried out on persons exposed in industry.

The animals were divided into 2 groups, one exposed to 0·05 and the other to 0·005 mgm. per litre; both groups were exposed for 5 hours a day for 6 months. Control groups were also kept. The rats exposed to the higher concentration showed changes in the motor-food-conditioned reflexes after two weeks. These returned to normal 2 months after the end of exposure. Those exposed to the lower concentration showed insignificant changes, differing only slightly from the controls after 3 months. The electroencephalogram was recorded with permanent indwelling extradural bipolar electrodes. Care was taken to ensure that the animals were accustomed to the experimental set-up. The higher concentration of trichloroethylene produced, after two weeks, evidence of " excitation " and after further exposure the amplitude of the fast waves lessened and their frequency was diminished. These changes indicated a " lowering of the efficiency of the cells of the cerebral cortex." This test was not, apparently, carried out at the lower, concentration, 0·005 mgm. per litre. Histological investigation showed changes in the pyramidal cells of the cortex in the first group, but in the second group the morphological changes were hardly noticeable.

During this time the urinary content of trichloroacetic acid (TCA) and of trichloroethanol (TCE) were determined weekly by the methods of Soucek and Vlachová in 24-hour samples of urine. In the first group the TCA varied from 0·09 to 0·48 mgm. per litre and in the second group from 0·0 to 0·13, but was only detected toward the end of the fifth month, then inconsistantly. TCE in urine in the first group was about 206 mgm. per litre, there was a slight rise in the amount excreted as the length of exposure increased. In the second group the TCE was not detectable until after 3½ months and then only about 50 mgm. per litre, this latter is considered a safe level.

Clinical investigation was carried out on workers using trichloroethylene for degreasing radio components. The content in the air was close to the permissible level or lower but for short intervals (when the baskets with washed components were carried—15 to 30 seconds) it rose to 0·06 to 0·2 mgm. per litre. Those workers exhibiting a mild degree of intoxication had 100 mgm. per litre of metabolites (TCE 75 mgm. per litre). Where the intoxication was moderate and pronounced the total amount of trichloroethanol and trichloroacetic acid was 200 mgm. per litre and higher. The TCA in workers with signs of intoxication varied from 12 to 135 mgm. per litre. In healthy women workers the amount of metabolites did not exceed 60 mgm. per litre.

[Unfortunately the account of the clinical investigation is limited to two paragraphs at the end and no details are given.] *W. R. Lee*

Stack, V. T., Jr., Forrest, D. E. & Wahl, K. K. **Determination of Trichloroethylene in Air.** *Amer. Indust. Hyg. Ass. J.* 1961, June, v. 22, No. 3, 184–6, 1 fig.

This paper contains the details of a method for determining the concentration of trichloroethylene in air, based on the Fujiwara pyridine-alkali reaction, which is claimed to be both sensitive and accurate. There are descriptions of the sampling of the air with a 250 ml. sampling tube; extraction of trichloroethylene by toluene; the reagents—toluene, dry pyridine, 1% ethanolic potassium hydroxide, methanol and standard trichloroethylene solution; the subsequent procedure and measurement of optical density; calibration and calculation.

It is stated that the procedure, as described, " will detect one microgram of trichloroethylene in the aliquot analyzed and can be used to determine trichloroethylene concentrations in air as low as one part per million by volume using a 250 ml. air sample." *M. E. Delafield*

Gordienko, E. A. **[Comparison of Changes in the Cerebral Metabolism during Hypoxia and Carbon Monoxide Intoxication]** *Gigiena Truda i Professional'nye Zabolevaniya.* Moscow. 1961, v. 5, No. 3, 19–23, 2 figs. [16 refs.] [In Russian.] English summary.

Previous work by this author had shown that after acute or subacute exposure to CO there was in experimental animals an increase in the concentration of ammonia in the brain together with a fall in amide nitrogen of the brain tissue. Possible reasons for this are (1) direct action of the CO, (2) oxygen deprivation, (3) effect on other organisms with secondary effect on cerebral metabolism.

The method is described in detail in the paper. White rats (200–250 gm.) were rendered hypoxic by inhalation of a mixture 5–7% oxygen with 93–95% nitrogen for about 1 to 3 days. They were killed and estimations of the following substances were made on brains: ammonia, glutamine, amide nitrogen of protein together with adenosine triphosphoric acid (ATP) and glycogen.

The content of ammonia and glutamine was increased above normal controls, the amide nitrogen was within normal limits. These changes are stated to be comparable with those found in CO poisoning.

The glycogen and ATP content of brains after acute CO poisoning (1–3 hours at 2–5 mgm. per litre) and subacute poisoning (24–48 hours at 0·5–0·7 mgm. per litre) are compared with the findings in hypoxia. The ATP (readily hydrolysed phosphorus) rose in CO poisoning but fell in anoxia. The glycogen content of the brain was unaffected by CO poisoning despite the agonal state of the animals, whereas this constituent is stated to be decreased in hypoxia.

A source of energy in brain metabolism is the conversion of ammonia and glutamic acid to glutamine by the action of ATP.

It is postulated that in CO poisoning there is a blockage of subsequent utilization, whereas in hypoxia the nitrogenous substances accumulate owing to the " frank defect of energy " [presumably associated with the decrease in ATP and glycogen].

The important conclusion is drawn that CO has a direct poisoning action on brain metabolism and does not depend for its effect on hypoxia alone. *W. R. Lee*

BREYSSE, P. A. **Hydrogen Sulfide Fatality in a Poultry Feather Fertilizer Plant.** *Amer. Indust. Hyg. Ass. J.* 1961, June, v. 22, No. 3, 220–22, 1 fig.

" Hydrogen sulfide is important to industry because of its nuisance value more often than its usefulness." A short account of the toxicology of this dangerous substance and mention of the industries in which it is a waste product and of its evolution in putrefactive processes precede a report on a fatal case of poisoning.

The plant in which the fatality occurred manufactured fertilizer from poultry feathers. These were boiled in a steam cooker to soften them. Steam and liquids were then aspirated from the boiler through a pipe which discharged into a pond. The feathers were dried, ground and bagged.

The man who died was found lying over the discharge pipe near the pond and it is evident that he had been trying to plug a leak in this pipe when he was overcome by the issuing gas. At autopsy bilateral marked haemorrhagic pulmonary oedema, cyanotic appearance of brain and skin of the head and cerebral oedema were found. Laboratory examination of the blood showed that hydrogen sulphide was present but the test for sulphmethaemoglobin was inconclusive.

A survey of the plant was made to determine hydrogen sulphide concentrations at different points and at different stages in the process. A table gives the results. It was found that up to 4,000 parts of hydrogen sulphide per million were present at times in the air close to the rupture in the outfall line.

M. E. Delafield

PISANI, F. & ANFOSSI, F. Intossicazione acute da composti fluorurati. [**Acute Poisoning by Fluorinated Compounds**] *Med. d. Lavoro.* 1961, Mar., v. 52, No. 3, 196–204, 3 figs. English summary (9 lines).

As a result of a leak in the coil of a condenser which was being used for the distillation of fluorinated compounds the gases within it escaped along with the water which was being used for cooling purposes and as a result workmen who were employed in the neighbourhood inhaled these substances. Many of them were very ill and the case histories of 6 are described in detail. The symptoms followed the same pattern in all six cases: an hour or two after having inhaled the gas those affected experienced a bitter taste in the mouth, severe weakness, tightness in the chest with a feeling of suffocation, tremor and heaviness in the head. 2 of the 6 patients were disorientated and 1 or 2 hours later severe dyspnoea occurred with coughing attacks unrelieved by treatment. The temperature was raised in varying amounts but subsided after a few days but the general condition of the patients remained far from good for many weeks with persistence of intense weakness, headache and shortness of breath on the least exertion. The X-ray appearances in the lungs showed the presence of widespread small foci of increased density similar to those seen in bronchopneumonia, chiefly involving the middle and lower zones on both sides and accompanied by emphysema. The radiological picture gradually improved although changes were still to be seen when the lung condition had resolved clinically. The ocular fundi showed considerable dilatation and tortuosity of the retinal veins with involvement of the optic nerve in 2 cases. Blood counts showed a relative leucocytosis immediate or delayed in all subjects, in most of whom red cells were also reduced in number.

References in the literature to acute toxic effects following exposure to risk of this kind occurring in man have been few and accurate descriptions have been limited to experimental intoxication in animals. Effects induced in guineapigs after prolonged exposure included pulmonary oedema in a certain proportion of animals but deaths did not occur from this cause in larger creatures such as dogs and monkeys. BARTALINI and GRIANTI (*Proc. 11th International Congress on Occupational Health, Naples,* 1954) described similar clinical appearances in subacute intoxication coming on 4-6 hours after work but in their cases resolution took place after an hour or two. On the other hand American authors describe severe pulmonary oedema as a result of intoxication following accidental inhalation with a fatal outcome within a short space of time. As a result of this experience the authors are of the opinion that the inhalation of these compounds even in large amounts " does not imply dramatic situations as has been shown experimentally and as Foulger has stated " [abstracter's translation]. Prevention is essentially technical in character so that these compounds do not pollute the working environment. People who have previously suffered from serious disease of the respiratory system should not be employed in work exposing them to a risk of this kind.

[The description of the process is too meagre to enable an adequate opinion to be formed about the risk to which these men were subjected. It sounds as though they might have been exposed to the effect of phosgene or chlorine. This could have happened if one of the chlorine/fluorine derivatives of ethane or methane was in course of preparation and had come into contact with heat which might cause these gases to be liberated. Alternatively fluorine might have been present in uncombined form at some stage of the process.

G. F. Keatinge

DANISHEVSKY, S. L. & KOGANOV, M. M. [**The Toxicology of some Fluoro-Organic Compounds**] *Gigiena Truda i Professional'nye Zabolevaniya.* Moscow. 1961, v. 5, No. 3, 3–8, 2 figs. [12 refs.] [In Russian.] English summary.

The toxic properties of fluorolefines in industrial conditions are to a considerable extent due to the presence, in technical products, of toxic admixtures. Thus the toxicity of vinylidine fluoride for white rats was 2 mgm. per litre from one sample while 2096 mgm. per litre from another produced no noticeable change, the lethal concentrations of 4 samples of hexafluorpropylene for white rats were 20, 45, 60 and 82·5 mgm. per litre. The toxicity of hexafluorpropylene may be due to the presence of perfluorisobutylene. Practically pure perfluorisobutylene in a concentration of 0·015 mgm. per litre caused death of all the animals (white rats) while the technical product, containing about 41% perfluorisobutylene had the same toxic effect at 0.035 mgm. per litre, whereas perfluorbutenes, purified from perfluorisobutylene, caused no deaths, even at 40 mgm. per litre.

Pathological investigation of perfluorisobutylene poisoning showed acute vascular disorders of the internal organs, especially the lungs and kidneys, but also in the the spleen and liver. The cells of the bronchial epithelium were "compact" and there was leucocytic infiltration of the bronchial walls and of the peribronchial tissue, indicating the chemical nature of the injury. Similar changes are observed in acute poisoning by hexafluorpropylene, tetra fluorethylene and trifluormonochlorethylene. The effects of repeated acute poisonings are briefly described. They include hypoglycaemia with altered sugar tolerance and "reduced phosphatase activity of the blood."

A possible mechanism for the biological action of fluoridized olefins is discussed. At normal temperature oxidation can take place with subsequent hydrolysis of the substances formed, thus trifluoromonochloroethylene can give rise to fluorphosgene, hydrogen fluoride, oxalic acid and hydrogen chloride. Similar changes may take place in the human body, the histopathological changes are explained by the action of hydrogen fluoride and oxalic acid.

The thermal decomposition of polymers is discussed, the following substances being identified: tetrafluorethylene, hexafluorpropylene, octofluorcyclobutane, perfluorisobutylene together with fluorphosgene, fluorchlorphosgene, HF HCl and a series of other volatile low-molecular saturated and unsaturated fluoro-organic compounds [a number of references are given to this work]. The pathological picture resulting from inhalation of thermal decomposition products of fluoroplastics basically resembles that seen by poisoning by perfluorisobutlyene and other fluorosubstituted olefines.

W. R. Lee

READ, Sheila T. & MCKINLEY, W. P. **DDT and DDE Content of Human Fat. A Survey.** *Arch. Environment. Health.* Chicago. 1961, Aug., v. 3, No. 2, 209–11. [11 refs.]

Abdominal fat from 62 patients in Canadian hospitals in 3 provinces was analysed for its content of DDT and the dehydrochlorinated derivative DDE (2,2-bis-[*p*-chlorophenyl]-1,1-dichloroethylene). The levels found were as follows:—

0 p.p.m.	1 case
2–5 „	47 cases
6–9 „	11 „
10–14·3 p.p.m.	3 „

The proportion stored as DDE ranged from 28 to 90%. There were no differences in figures among the sexes or different age-groups or in those from the three regions. [No reference is made to any occupational or domestic exposure to DDT. It is assumed that the subjects had received the DDT or DDE in their food.]

J. M. Barnes

CAVANAGH, J. B., DAVIES, D. R., HOLLAND, P. & LANCASTER, M. **Comparison of the Functional Effects of Dyflos, Tri-*o*-Cresyl Phosphate and Tri-*p*-Ethylphenyl Phosphate in Chickens.** *Brit. J. Pharmacol. & Chemotherapy.* 1961, Aug., v. 17, No. 1, 21–7.

The signs of neurotoxic damage in hens poisoned by di-isopropyl phosphofluoridate [dyflos], tri-*ortho*-cresyl phosphate and tri-*para*-ethylphenyl phosphate are described and compared. The compounds were given either by mouth or by intramuscular injection.

With each there is a latent period of 8–18 days between giving the dose and the appearance of the signs of neurotoxic damage. Tri-*p*-ethylphenyl phosphate differs from the two other compounds in not producing any inhibition of cholinesterase in poisoned birds. It produces a somewhat different picture of ataxia, for example, a high-stepping gait is more often seen, and histologically there is relatively more damage to the peripheral nerves than to the tracts in the spinal cord after tri-*p*-ethylphenyl phosphate than after the other compounds. *J. M. Barnes*

FREDRIKSSON, T. **Percutaneous Absorption of Parathion and Paraoxon. IV. Decontamination of Human Skin from Parathion.** *Arch. Environment. Health.* Chicago. 1961, Aug., v. 3, No. 2, 185–8. [17 refs.]

^{32}P–labelled parathion free from ^{32}P–labelled contaminants was included in an emulsion containing 2% parathion. 0·1 ml. was applied to 12 cm^2 of skin of the back of the hand. Radioactivity was determined by placing the hand at intervals under a suitably constructed counter. The hands were washed for 30 seconds with soap under running water and dried. After counting, the skin was cleaned for 15 seconds with 95% alcohol. After a further count the washing was repeated. When decontamination was carried out 30 minutes after applying the parathion 80% or more of the insecticide was removed by the first wash and practically all the remainder by the further treatment. If left for 300 minutes only one-half to two-thirds of the parathion was removed by the first wash. The alcohol cleansing removed about 90%.

It is concluded that parathion is steadily penetrating the skin, making its removal by soap and water progressively more difficult, though alcohol which is a good solvent for parathion is more effective. The need for better decontamination procedures for the skin in preventing parathion poisoning is stressed.

J. M. Barnes

JACOBZINER, H. & RAYBIN, H. W. **Parathion Poisoning successfully treated with 2-PAM (Pralidoxime Chloride).** *New England J. of Med.* 1961, Aug. 31, v. 265, No. 9, 436–7.

PÎSLARU, V. Date experimentale cu privire la toxicitatea insecticidului "Cebetox". [**Experimental Data on the Toxicity of Cebetox Insecticide**] *Igiena.* Bucharest. 1961, Jan.–Mar., v. 10, No. 1, 27–31.

The author has investigated the acute toxicity of Cebetox (O,O,dimethylmercaptomethyl thiophosphate) [a methyl analogue of demeton-S], a contact insecticide used in agriculture. Appropriate dilutions of the commercial 20% solution were injected intraperitoneally

into groups of 10 mice, rats and guineapigs, giving a range of doses of 0·01–10 mgm. per kgm. The LD50 for all 3 species lay between 0·5 and 0·7 mgm. per kgm. The toxicity of the solutions declined rapidly on keeping.

D. J. Bauer

Bull. World Health Organization. Geneva. 1961, v. 24, Nos. 4/5, 611–49, 18 figs. [Numerous refs.]
Disinsection of Aircraft with DDVP.

[An abstract of this paper appeared in the *Tropical Diseases Bullein*, 1961, v. 58, 1401.]

Abe, J., Inui, S. & Morimoto, S. **[Surveys on Occupational Dermatitis in a Copper Wire Factory]** *Japanese J. Nation's Health.* 1961, Mar., v. 30, No. 1, 30–34, 2 figs. [In Japanese.]

The English summary appended to the paper is as follows:—

"The workers in making copper wire and powder often complain of a sweet taste in the mouth and their shirts become green in colour. Only a few reports have been informed, however, about dermatitis due to copper. Survey was undertaken into the occupational history, subjective symptoms and others of copper dermatitis using investigational cards for 159 workers who were extending, drawing, rolling, polishing, grinding and packing processes of electric copper (99.9 per cent pure) and 47 workers who handled pure copper powder. Patch test was applied, furthermore, for the purpose of excluding those who were sensitive to copper. The results were as follows:

"Among 206 workers, 155 (75·1%) have experienced copper dermatitis. Past history of the disease was more frequent in workers with powder than wire. Red acne was found according to hair follicles from May to July, and almost disappeared from August to October. As for the result of patch tests for 151 workers, 45 workers (29·9%) were positive, 33 (21·8%) doubtful, and 73 (48·3%) negative. The reactions to the test were slight in those who were exposed to copper dust without dermatitis for long periods and those who continued to work with copper after recovery from the disease, but were often positive in those who were removed from copper dust after recovery.

"In this survey, it was demonstrated that copper powder might cause dermatitis."

Medical Res. Council. **Maximum Permissible Contamination of Respirable Air after an Accidental Release of Radioiodine, Radiostrontium, and Caesium-137. Report to the Medical Research Council by its Committee on Protection against Ionizing Radiations.** *Brit. Med. J.* 1961, Aug. 26, 576–9. [22 refs.]

The Council's first Report on maximum permissible dietary contamination in 1959 was followed in 1960 by one upon the problems of exposure to beta and gamma radiation if radioactive material was dispersed by accident at atomic energy installations [this *Bulletin*, 1961 v. 36, 342]. The present Report deals with the problem of exposure from radioactive material which might be inhaled during the passage of a cloud of such material.

The regions of the body considered most vital in this respect are the thyroid owing to its selective absorption of radioiodine, the bone and bone marrow because of the selective deposition therein of radiostrontium and the body as a whole for radiocaesium. The selective behaviour of these 3 radioactive substances not only operates as stated but their quantitative significance in the body depends upon age. This is well brought out in the data on p. 576 which list the maximum permissible total intakes at birth, 6 months, 1 year and adult life.

It is well to put on record the extraordinary degree to which these quantitative recommendations run parallel to those of the International Commission on Radiological protection in their reports for 1958 [this *Bulletin*, 1959, v. 34, 648] and 1959. Although the terms of reference of the two bodies concerned were not identical there was a substantial field of investigation which was common to them and it is for this reason that a comparison between data can be made. It leads to the view that the recommendations have a sound quantitative basis.

S. Russ

Bair, W. J. & McClanahan, B. J. **Plutonium Inhalation Studies. II. Excretion and Translocation of Inhaled $Pu^{239}O_2$ Dust.** *Arch. Environment. Health.* Chicago. 1961, June, v. 2, No. 6, 648–55, 4 figs. [12 refs.]

How does an animal get rid of inhaled plutonium oxide? The answer depends both on the animal (rats, mice and dogs have been tested) and on the size of the dust particles inhaled.

The present work was carried out on 4 dogs and though this appears a small number upon which to draw conclusions, this is offset by the detailed character of the tests carried out. Any specified amount of dust inhaled is deposited in the lungs to the extent of about 75%, the remainder getting into the upper respiratory tract and the intestinal tract, whence it is eliminated. Examination of the faeces and urine was systematically carried out.

Plutonium oxide is very insoluble; once deposited in the lung it is not eliminated by solution processes but by the lymphatic system, lavage not solution. This clearance is apparently more rapid in rats and mice than in dogs.

Plutonium is a dangerous substance for the body tissues with which it comes into contact; fortunately it is not deposited in bone and the comparatively rapid elimination when it is introduced into the lung is a big element making for safety.

S. Russ

Food and Nutrition

The order in this section is:—**General; Foodstuffs; Food Poisoning.**

FOODSTUFFS

(Composition and Bacteriological Control)

NORTH, W. R., Jr. **Lactose-Pre-Enrichment Method for Isolation of *Salmonella* from Dried Egg Albumen. Its Use in a Survey of Commercially Produced Albumen.** *Applied Microbiol.* Baltimore. 1961, May, v. 9, No. 3, 188–95. [13 refs.]

Lactose broth was used for the pre-enrichment of commercially produced dried egg white before inoculation of selective media. Naturally infected dried albumin was suspended in sterile lactose broth in jars and tubes for a salmonella count by a modified "most probable numbers" (MPN) technique. Tubes and jars were incubated for 24 hours at 35°C. Tubes showing growth were subcultured into 1·0 ml. quantities of selenite cystine (SC) medium in small tubes incubated at 35°C. for 6–7 hours and streaked onto *Salmonella-Shigella* (SS), brilliant green and bismuth sulphite agars. After a further 24-hour period the SC cultures were replated if necessary. For comparison with direct enrichment procedures, 3 liquid media were used, 2 modifications of tetrathionate (TT), and selenite cystine, subcultured on to SS and bismuth sulphite agars.

SC gave better results than either of the TT media after 24 hours' incubation, but both media, and particularly TT, gave higher positives after 48 hours. There was a marked increase in MPN isolations by the lactose broth pre-enrichment method over direct inoculation into any enrichment medium. Inhibitory enrichment media can be selective of species and encourage those which are less susceptible. Similar results were obtained with two highly contaminated but naturally infected samples. The pre-enrichment method was also superior to centrifugation methods.

Of 79 samples of dried egg white from 11 drying plants, 30 were positive for salmonellae, $3{\cdot}6\text{–}1{\cdot}1 \times 10^9$ per gm.; most of the positive samples came from a few manufacturers whose products were highly contaminated; the inoculation of fermented albumin from batch to batch increased contamination.

The rise in reported cases of salmonellosis in 1959 and the occasional association of egg products made it necessary to detect small numbers of salmonellae; the danger of egg albumin in lightly-cooked foods in which salmonellae survive and subsequently multiply is pointed out. *Betty C. Hobbs*

WEADON, D. B. **A Technique for the Isolation of Heat Resistant *Cl. welchii* from Meat.** *J. Med. Lab. Technol.* 1961, Apr., v. 18, No. 2, 114–16.

714 samples of meat including beef, lamb and pork were obtained from wholesale and retail butchers' premises and from an abattoir.

25 gm. of meat in 2 oz. wide-mouth screw-capped jars were covered with nutrient broth and boiled for 1 hour in a shallow bath; cooled and incubated at 37°C. for 18–24 hours.

Three drops of broth suspension from beneath the meat were placed on the surface of a modified Neomycin Nagler plate, spread, and incubated anaerobically at 37°C. for 24 hours; 8 samples were examined on one plate. Colonies showing good lecithinase activity were subcultured to another Neomycin Nagler plate to test (1) specific neutralization of lecithinase reaction by *Clostridium welchii* type A antitoxin, and (2) possible aerobic growth.

Tubes of lactose agar were also inoculated to confirm fermentation by *Cl. welchii* and to differentiate from the lactose-negative *Cl. bifermentans*.

Heat-resistant *Cl. welchii* were isolated from 130 (18·2%) samples of meat *Betty C. Hobbs*

ANDERSON, K. & WOODRUFF, P. **The Bacteriological Screening of Desiccated Coconut.** *Med. J. Australia.* 1961, June 10, v. 1, No. 23, 856–8, 2 figs.

Experiments carried out during the routine testing of desiccated coconut for salmonellae indicated that the screening technique was inadequate and that contaminated batches were sometimes passed for human consumption. 10% sampling took place after unloading, and for routine examination 20 gm. quantities of coconut were incubated in selenite F medium and subcultured onto SS agar (Difco) after 18 hours. Suspicious colonies were tested by the usual biochemical and serological methods. The contamination was found to be scanty and unevenly distributed and the examination of a particular sack showed that one only of 29 samples was positive. When 1,800 gm. of coconut from the same sack were packed in a cylinder and 2 litres of selenite allowed to percolate through, 150 ml. of turbid fluid from the first litre were negative, whereas 600 ml. from the second litre were positive, also 180-gm. samples in selenite gave more positive results than 20-gm. samples.

In artificially contaminated coconut, Salm. Thompson was destroyed in "pyramids" baked at 200°F. for 60 minutes, and "squares" baked at 350°F. for 15 minutes, but survived in the uncooked nut for at least 4 weeks.

The importation of this food is a matter of concern to the public health authorities. Methods of treatment are discussed. *Betty C. Hobbs*

GÄRTNER, H. & BÖHLCK, I. Kokosraspeln als Infektionsquelle für Paratyphus-Erkrankungen. **[Coconut as a Source of Paratyphoid Infections]** *Deut. med. Woch.* 1961, Aug. 25, v. 86, No. 34, 1609–10, 1634.

Since the reports from England in 1959 and 1960 of the isolation of 76 strains of paratyphoid and enteritis

bacteria from 851 samples of coconut imported mainly from Ceylon [this *Bulletin*, 1960, v. 35, 1184: 1961, v. 36, 128], investigations in Germany have yielded similar results [*ibid.*, 1961, v. 36, 347].

This paper records the results of the examination of 340 samples of coconut and 15 samples of baked cakes containing coconut at Kiel university. A total of 19 isolations of salmonella organisms were made from these samples, in 1 case from macaroons. The types of these organisms were S. java (4), S. Senftenberg (4), S. Bareilly (4), S. Butantan (2), *S. typhi-murium* (1), S. Stanley (1), S. Litchfield (1), S. Chingola (1), and S. Hvittingfoss (1). Reference is made to the findings of other work carried out in Germany.

These isolations have been mainly of so-called rare salmonella types which appear to have but small power of spread; nevertheless all that is possible should be done to prevent their importation and naturalization.

M. E. Delafield

Clark, W. S., Jr., Moore, T. D. & Nelson, F. E. **Characterization of Coagulase-Positive Staphylococci isolated from Raw-Milk.** *Applied Microbiol.* Baltimore. 1961, May, v. 9, No. 3, 195–9. [22 refs.]

19 raw milk samples (March-May) and 20 samples of Grade A milk (June-August) were plated on a modified tellurite-glycine medium. Black colonies were checked by the tube coagulase test and 62 isolations were made. In 58% of the samples where 2 or more isolations were made, more than one strain of coagulase-positive staphylococci was obtained. Pigmentation, mannitol fermentation, gelatin hydrolysis, lipolytic activity, haemolysin production and antibiotic sensitivity were determined; all the strains were phage typed, and 6 were tested for enterotoxin by intraperitoneal inoculation into kittens.

Mannitol fermentation and coagulase production were both characteristic of most of the cultures, but there was no control group of coagulase-negative strains. 6 strains failed to hydrolyse gelatin. Pigment production varied from golden to white; the only strain demonstrated to be enterotoxigenic was non-pigmented. 10 of 21 strains were lipolytic, 30 strains produced both α and β haemolysis, 19 β haemolysis only, and 2 α haemolysis only. 25 strains were sensitive to bacteriophage types indicative of bovine strains; 9 strains were sensitive solely to bacteriophage of human type and 10 were sensitive to both human and animal types; 7 strains were untypeable. No relationship was shown between the patterns of lysis by bacteriophage, and haemolysin production. The one enterotoxigenic strain, of the 6 tested, was lysed by bacteriophage 6. All strains tested were sensitive to the concentration of antibiotics found in Difco Bacto-sensitivity discs.

The staphylococci commonly found in raw milk possessed characteristics sometimes associated with those of human strains and sometimes with those of bovine strains, but correlation between the various characteristics studied was at a relatively low level. *Betty C. Hobbs*

World Health Organization. Technical Report Ser. No. 220. **Evaluation of the Carcinogenic Hazards of Food Additives. Fifth Report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva, 12–19 December 1960.** 33 pp. [Numerous refs.] 1961. Geneva: Palais des Nations. [Sales agent for U.K., H.M. Stationery Office.] [3s. 6d.; $0.60; Sw.fr. 2.–.] [Issued also as *FAO Nutrition Meetings Report Ser.* No. 29.]

This meeting was the fifth of a series of joint FAO/WHO expert committee meetings beginning in 1955, and concerned with problems governing the use of food additives. The present meeting was convened in accordance with a recommendation of an earlier FAO/WHO committee in 1957 that a group of experts should consider the possible carcinogenic effects of food additives. The committee consisting of twelve members, met in December 1960, with Professor A. C. Frazer (United Kingdom) and Mr. H. Van Genderen (Netherlands) as Chairman and Vice-Chairman respectively. Its terms of reference were to consider the evaluation of carcinogenic hazards of food additives. Under the heading of additives were included food contaminants and certain naturally occurring substances.

The committee adopted the principle that "the use of certain food additives is justified since the present position with respect to world food supplies makes it imperative that good technological procedures should be developed and used to a maximum extent". It insisted, however, that all such substances, now in use or to be used in future, must be subjected to adequate testing to ensure minimum risk to the consumer. It further emphasized that the presence of carcinogens in foods might be a significant factor in the causation of cancer in man and that reduction of such substances to their lowest practicable level might contribute to the prevention of cancer.

In recent years a number of substances in foods, including some natural constituents and even an essential nutrient like selenium, have been suspected of having carcinogenic properties. However, the evidence for the carcinogenicity of many of these substances is not convincing. The committee therefore limited its discussions almost completely to the testing of the carcinogenicity of suspect materials. The type of experimental animal to be used, the length of the test period, the basal diet and the means of administering the carcinogen were considered in detail. Difficulties of interpretation, such as those arising from the natural incidence of tumours in some species, the presence of unsuspected contaminants and the effects of nutrient and calorie intake were discussed. It was recognized that the results obtained in animal experiments were necessarily limited in their application to man and that therefore, notwithstanding the difficulties, human epidemiological studies should be an important part of the research programme on carcinogens.

The committee recommended that short duration tests should be done whenever possible to ensure testing of the maximum number of carcinogens. Much depended

on good experimental design and highly trained specialists, particularly animal pathologists, should be responsible for the interpretation of results. The report includes two annexes the second of which is a summary of the details considered desirable in investigations of carcinogenicity. Annex 1 summarizes some information already available on certain preservatives, food colours and contaminants. *Ruth Schwartz*

FOOD POISONING

EL GHOROURY, A. A. A. & ZAKI, M. H. **A Preliminary Survey of Food Handlers for Typhoid and Paratyphoid Carriers.** *J. Egyptian Pub. Health Ass.* 1961, v. 36, Nos. 1/2, 15–26. [12 refs.]

In the survey reported here 1,001 persons of ages varying from 13 to 72 years who lived within the area comprising the city of Alexandria and were engaged in some sort of food-handling were examined for evidence of the enteric carrier state. Urine and faeces samples from each person were examined bacteriologically and 982 persons were examined serologically for Vi agglutinins. Although 13·5% of 982 sera examined contained Vi agglutinins in titres of 1/10 or more, *Salmonella typhi* was not isolated from any specimen of stool or urine, but *Salm. paratyphi C* was present in the cultures of one stool specimen. There were probably 9 other strains of salmonellae among the organisms isolated from the faeces, but these were not identified. Of the 1,001 urine samples examined 933 were found to be sterile.

[In a country where typhoid fever is endemic (in 1959 there were 1,698 notified cases of enteric fever in Alexandria alone) one would have expected even a single examination of the stools to show the presence of some typhoid carriers. In the reviewer's experience of some 30 years ago in the Cairo area and that of MILLER in some of the Delta villages (see *J. Egyptian Pub. Health Ass.*, 1950, v. 25, 45) the carrier condition was quite common among unselected populations. But the population surveyed in this paper can hardly be said to be unselected: all but 5 of the 1,001 had a recent history of TAB inoculation (no information about the type of TAB vaccine) and only 12 of the total had any medical history which might suggest enteric fever. In other words this was rather a special population and though it is possible that 3 or more examinations of stool samples might have revealed the presence of some typhoid carriers the number would be likely to be below the general average. There is no information about the extent of the medical examination for these food handlers but it is presumed, in view of the fact that 93% had sterile urines, that no person in the series would have been accepted had he been suffering from schistosomiasis.

There is one further point of interest: the high proportion of sera showing Vi agglutinins in titres of 1/10 or more. This is not a unique observation in so far as Egyptian villagers are concerned (see Miller *loc. cit.*) and also ANDERSON, cited in a recent *Public Health Lab. Service Report* (see p. 1223) and it is no uncommon finding among the Egyptian population in general that a relatively high proportion of normal sera contain Vi agglutinins. In contrast with the Egyptian figure of 13·5%, a recent British survey (see *Pub. Health Lab. Service Report, loc. cit.*) on 343 normal sera, of which 75 came from TAB inoculated subjects, showed that only 1·17% of the total contained significant Vi agglutinins. It should be pointed out, however, that the British estimations of Vi antibody were made with standardized reagents and a fully controlled technique and the estimations recorded in the present paper were made with living suspensions of a "standard strain of *Salmonella typhi*" in Dryer's tubes and there is no mention of the inclusion of a standard Vi serum in the tests though positive and negative controls were included. The inclusion of a standard Vi serum—preferably the current Provisional Standard Serum for Vi agglutination originally introduced by FELIX (this *Bulletin*, 1939, v. 14, 344)—in all quantitative estimations of Vi agglutinins is so important that results of tests which did not employ the standard serum are not comparable. How much technique influenced the results obtained in the present survey it is not possible to say, but there seems to be little doubt that there are factors, at present not properly understood, which may influence, in certain populations, the development of low-titre Vi antibodies which seem to be unconnected directly with typhoid infections.]

H. J. Bensted

ANDERSON, E. S., GALBRAITH, N. S. & TAYLOR, C. E. D. **An Outbreak of Human Infection due to *Salmonella typhimurium* Phage-Type 20a associated with Infection in Calves.** *Lancet.* 1961, Apr. 22, 854–8, 2 figs. [14 refs.]

55 incidents with 90 cases of food poisoning due to *Salmonella typhi-murium* phage type 20a were reported from July to October 1958 in south-east England; there was 1 death.

Phage typing linked the cases together, and connected them with sick calves and their collecting centres and abattoirs.

The incubation period varied from 24–84 hours; most patients had fever, malaise and diarrhoea, and some had abdominal pain. Calf meat was the most probable vehicle of infection in at least three-fifths of the incidents.

An examination of 1,127 calves direct from farms in the area concerned showed a *Salm. typhi-murium* infection rate of less than 0·5%. In calves slaughtered at two London abattoirs, after they had been kept together at the collecting centres for 2–5 days, the infection rate was 35·6% (12·7% were *Salm. typhi-murium* phage type 20a), in contrast to calves collected together for a few hours only when the infection rate was 0·6%; thus

cross-infection appears to be an important factor in the proportion of carrier animals.

9 of 84 calves' palates from a butcher's shop were positive for salmonellae, 8 were *Salm. typhi-murium* phage type 20a and 1 was Salm. Bredeney. *Betty C. Hobbs*

Cust, G. & Finch, J. W. **An Outbreak of Staphylococcal Food Poisoning.** *Med. Officer.* 1961, Aug. 11, v. 106, No. 6, 98–9.

Approximately 32 people, mostly from a women's club outing, were taken ill with severe vomiting and diarrhoea 3–4 hours after lunch at a cafe. *Staphylococcus aureus* was isolated from swabs of an infected finger sore and the nose of the chef who handled the food; the same phage type was found in samples of chicken meat left over from the meal but recovered from the waste bin, and also from patients' vomit and faeces. The antibiotic sensitivity patterns of all these strains were the same. Chicken, beef, and lamb had been cooked the previous day, placed in the refrigerator overnight, and carved early next morning. The sliced meat on plates was allowed to stand for about 3 hours in the kitchen before being warmed up on the hot plate 2 hours before lunch.

The chef's nose and finger were treated with an ointment containing neomycin and bacitracin until 3 negative swabs were obtained; he was away from work for 11 days and was still under observation. Kitchen inspection and discussions with the staff resulted in improved food hygiene. *Betty C. Hobbs*

Cavanagh, J. B. & MacDermot, Violet. **Sensory Terminal Degeneration in Ortho-Cresyl Phosphate Poisoning.** *Lancet.* 1961, Sept. 9, 583–4, 3 figs.

Mycoses and Mycology

The order of diseases and fungi in this section is:—**General; Dermatophytes; Blastomyces; Histoplasma, Sporotrichum, Phialophora; Candida, Cryptococcus; Actinomyces, Nocardia; Aspergillus; Others.**

Papers on Blastomycosis (South American type), Coccidioidomycosis, Mycetoma and Rhinosporidiosis are abstracted in the TROPICAL DISEASES BULLETIN.

Mahnke, P. F., Zschoch, H. & Sichert, H. Pilzbefunde im Tracheobronchialbaum des Menschen. Häufigkeit, Arten und pathogenetische Bedeutung. **[Incidence, Species and Possible Pathogenicity of Fungi found in the Bronchial Tree]** *Pathologia et Microbiol.* Basle. 1961, v. 24, No. 3, 327–40. [80 refs.]

The English summary appended to the paper is as follows:—

"Systematic post mortem examinations of the bronchial tree established the presence of fungi in close to 50% of 375 cases. Candida albicans, tropicalis, krusei, pseudotropicalis, zeylanoides, stellatoidea, Saccharomyces fragilis, fructum and oviformis as well as Torulopsis glabrata were cultured and identified.

"Histological studies did not reveal any tracheobronchial mycoses. The possible rôle of fungi as pathogens is discussed, with special consideration of local candidiasis. Based on published evidence, all of the identified fungi are considered to be potentially pathogenic."

Sado, T., Miyamoto, F., Yano, K., Sako, I., Ose, H. & Watanabe, J. **Studies on the Antibacterial and Antifungal Substances. Part I. On a New Antifungal Organic Mercurial, Methylmercurithioacetamide.** *Agricultural & Biol. Chem.* Tokyo. 1961, Feb., v. 25, No. 2, 77–82. [13 refs.]

These authors have prepared 19 new alkylmercurithio derivatives, and determined their minimum inhibitory concentrations for 5 species of bacteria and 4 of fungi. All were more active than Thimerosal (sodium ethylmercurithiosalicylate), and the highest activity (all species inhibited by 0·5 μgm. per ml. or less) was shown by methylmercurithioacetamide: this activity was reduced only 2- to 8-fold by 10% serum. Solutions of this compound are stable. It was successful in treating experimental *Trichophyton asteroides* infection of guineapig skin [as judged by cultivating pieces of skin after 10 days' application: it is not mentioned that the medium contained any neutralizer]. Toxicity tests were carried out in mice and rabbits. Application of a 0·2% solution to human skin for 21 days caused no ill effects. It is believed that this compound will prove valuable for the treatment of superficial mycoses. *L. P. Garrod*

Klite, P. D. & Gale, G. R. **An Antifungal Substance from *Pseudomonas aeruginosa.*** *Antibiotics & Chemotherapy.* New York. 1961, Apr., v. 11, No. 4, 256–60, 2 figs. [11 refs.]

One possible explanation of the overgrowth of *Candida albicans* in the bowel during antibiotic treatment is that some bacterium is suppressed which normally forms an inhibitory substance. Cultures of 8 aerobic (coliform) and 6 anaerobic intestinal bacteria (*Bacteroides* etc.), were tested for this by placing discs soaked in them on

Sabouraud plates inoculated with *C. albicans*. Of all these organisms only *Pseudomonas pyocyanea* produced a zone of partial inhibition, the colonies near the disc being smaller. There appears to have been a more distinct effect on many of 12 other pathogenic fungi, the illustrations showing wide zones of complete inhibition. Attempts to extract the inhibitory substance failed, and Seitz filtration inactivated it. [The authors do not discuss the possible identity of this substance with "pyocyanase". They mention no similar tests of other common intestinal bacteria: in pursuance of their hypothesis it seems necessary also to examine species of *Streptococcus*, *Clostridium* and particularly *Lactobacillus*, the latter having been credited, rightly or not, with just the action in which the authors are interested.]

L. P. Garrod

i. THIRUMALACHAR, M. J., MENON, S. K. & BHATT, V. V. **Hamycin, a New Antifungal Antibiotic. I. Discovery and Biological Studies.** *Hindustan Antibiotics Bull.* Pimpri. 1961, May, v. 3, No. 4, 136–8.

ii. BHATE, D. S., AMBEKAR, G. R., BHATNAGAR, K. K. & HULYALKAR, R. K. **II. Isolation and Chemical Properties.** *Ibid.*, 139–43, 2 figs. [23 refs.]

i. These papers are from the Research Laboratories of Hindustan Antibiotics Ltd. (a Government of India undertaking), who publish the journal in which they appear. Hamycin is obtained from *Streptomyces pimprina*, which was isolated from local soil. The characters of this organism are described. Activity against 24 fungi was examined: it was highest against yeast-like fungi (considerably greater than that of nystatin, with which it is compared) and against *Aspergillus niger*, whereas *Aspergillus fumigatus* is resistant.

ii. The second paper describes production, isolation and the physico-chemical properties of hamycin. It is a polyene (heptaene), amphoteric, and related to but clearly distinguishable from amphotericin B. *L. P. Garrod*

YARZÁBAL, L. A. Búsqueda de dermatófitos en 140 muestras de suelo del Uruguay. **[Investigation of Dermatophytes in 140 Uruguayan Soil Samples]** *An. Facul. de Med. Montevideo.* 1961, v. 46, Nos. 1/2, 41–6, 5 figs. [22 refs.]

The English summary appended to the paper is as follows:—

"In 140 soil samples in which the occurrence of keratin fungi was investigated, *M. gypseum* was isolated in 57 instances (40.1%) and *K. ajelloi*, in 36 (25%). Both appear to be evenly spread throughout Uruguayan territory. The fungi failed to show any special preference for any of the soils studied. Results are a further indication of the world-wide nature of both dermatophytes."

MANKTELOW, B. W. & RUSSELL, R. R. **Human Ringworm associated with *Trichophyton mentagrophytes*. Infection in Guinea Pigs.** *New Zealand Med. J.* 1960, Oct. v. 59, No. 338, 488–9, 4 figs.

As a result of 4 laboratory assistants developing ringworm, guineapigs which they had handled were investigated in a search for the aetiological agent. *Trichophyton mentagrophytes* was recovered from 31 of 32 guineapigs presenting with lesions and from 4 which did not show any lesions.

The possibility that frequent wetting of the skin and clothing might be a predisposing factor to infection is put forward by the authors. "Rigorous culling of all stock showing lesions" as well as the wearing of adequate protective clothing are control measures recommended.

C. J. La Touche

OSSWALD, M. Die cervico-faciale Aktinomykose und ihre moderne Behandlung. **[Cervico-facial Actinomycosis and its Modern Treatment]** *Ztschr. f. ärztl. Fortbildung.* 1961, May 15, v. 55, No. 10, 607–13, 22 figs.

This is a general account of the disease, dealing first with its aetiology. It is accepted that the infection is autogenous, and the author subscribes to Holm's belief that accompanying bacteria must contribute to the inflammatory process. There is some discussion of the precise portal of entry, with some (not very clear) dental skiagrams illustrating it. Literature on the sensitivity of *Actinomyces israeli* to antibiotics is reviewed, with emphasis on the fact that the organism is always sensitive to penicillin. The author has himself treated 17 cases with adequate follow-up: all were treated with penicillin (length of course not stated), the earlier ones also being given sulphafurazole and some of the later streptomycin. Short-wave diathermy was also used and is said to accelerate the reparative process: the last 6 figures are diagrams showing how this should be applied.

L. P. Garrod

SINSKI, J. T. **The Effectiveness of Pagano-Levin Medium for the Detection and Identification of *Candida albicans* in Clinical Specimens.** *J. Investigative Dermat.* 1960, Sept., v. 35, No. 3, 131–3.

For the purpose of assessing the efficacy of the Pagano-Levin culture medium [see also this *Bulletin*, 1960, v. 35, 1189] the author obtained 23 recently isolated but unidentified yeasts. These were grown on Nickerson-Mankowski agar for production of chlamydospores and on Pagano-Levin medium for observation of macroscopic cultural features. Those that gave a negative result for *Candida albicans* on these media were further tested in a fermentation series (glucose, maltose, sucrose and lactose).

Results included divergent reactions in 7 of the isolates. Of these, 4 were false positive on Pagano-Levin medium in so far as the results on this medium were not confirmed by those on Nickerson-Mankowski medium or by fermentation.

Accordingly, it is recommended that when absolute identification is desirable the other standard criteria should be invoked. *C. J. La Touche*

Lostia, G. B. Ulteriori ricerche sulle frazioni antigeni di *C. albicans.* [**Further Studies on Antigenic Fractions of *Candida albicans***] *Giorn. Batteriol., Virol. ed Immunol.* 1960, May–June, v. 53, Nos. 5/6, 226–34. [16 refs.] English summary.

Engel, M. F. **Monilial Granuloma with Hypergammaglobulinemia. Treatment with Amphotericin B and Dermabrasion.** *Arch. Dermat.* 1961, Aug., v. 84, No. 2, 192–8, 13 figs. [16 refs.]

Gamet, A. & Brunel, M. Observation peu commune d'un cas de moules bronchiques à *Candida albicans.* [**Rare Case of Bronchial Casts due to *Candida albicans***] *Bull. Soc. Path. Exot.* 1960, July–Aug., v. 53, No. 4, 644–50, 7 figs. on 4 pls. [11 refs.]

This article describes the first case of bronchial casts due to *Candida albicans* to be recorded in Africa.

The patient concerned, a woman aged 18 years, was admitted to hospital at Yaoundé for the first time on the 16th August 1957. At examination the only abnormal clinical feature was an excessively loud but regular heart beat devoid of murmurs or associated friction rub. Nevertheless, X-ray examination revealed a much enlarged heart. Because of the occurrence in Africa of cardiomegaly associated with deficiency diseases (that due to vitamin B1 in particular) therapy including vitamin B1, in addition to the administration of digitalin and mercurial diuretics, was instituted.

8 days after the commencement of treatment the patient coughed up a large, cylindrical, bifurcate, glistening white bronchial cast, bearing golden yellow nodules at the branched extremities of the 2 main branches. On microscopical examination this structure was found to consist of a large quantity of yeast and on culture yielded *Candida albicans.* Accordingly, additional treatment consisting of 10 tablets of nystatin daily, administered orally for 1 month, was instituted. The patient continued to produce similar casts for some time after the commencement of treatment, but these diminished in number until scarcely any were being produced. At the end of 2 months the patient discharged herself.

However, on the 8th of July 1959, owing to a relapse, the patient returned to hospital complaining of permanent cough in the course of which a copious, thick, grumous sputum was expectorated. Additional abnormalities were enlargement and induration of the liver and an associated slight ascites. During the first few days of this second period in hospital the patient expectorated another exceptionally large bronchial cast of a type similar to those recovered previously. Nystatin was re-instituted but without benefit, and, accordingly, penicillin in the dosage of 3 million units per day was substituted for this drug. However, despite these therapeutic measures the patient's condition remained unchanged and she was eventually removed from the hospital by her family.

C. J. La Touche

Hyun, B. H. & Collier, F. C. **Mycotic Endocarditis following Intracardiac Operations. Report of Four Cases.** *New England J. of Med.* 1960, Dec. 29, v. 263, No. 26, 1339–41, 3 figs. [35 refs.]

These cases had many features in common. All the patients concerned underwent operation for some form of valvular disease: aortic stenosis in 2, mitral stenosis in 1 and "calcific disease of the aortic valve complicated by angina pectoris" in the 4th. Sooner or later, during the post-operative period these patients developed symptoms and signs of infection, and accordingly, in some cases, were treated with antibiotics. This treatment was, however, ineffective, and when the real cause of infection, namely *Candida albicans,* was discovered, antifungal drugs were instituted. Even these drugs failed to arrest the progress of infection and all the patients died sooner or later. At autopsy thrombi or vegetations, or in some cases both, were found at the site of operation. These contained *C. albicans.* *C. J. La Touche*

Friedrich, E. & Bergmann, L. Das Aspergillom in mikrobiologischer Sicht. [**Aspergilloma, considered from a Microbiological Standpoint**] *Zent. f. Bakt.* I. Abt. Orig. 1961, v. 182, No. 4, 501–24, 13 figs. (2 coloured on pl.) [60 refs.]

The English summary appended to the paper is as follows:—

"The mycologic and bacteriologic examination results of sputa, punctates and aspergilloma contents obtained from autopsies are discussed in detail and information given about the serologic examination results.

"Evidence was found for the simultaneous, X-ray controlled development of tuberculosis and aspergillosis by the microscopic and cultural demonstration of M. tuberculosis and A. fumigatus. This is the first case, in which the simultaneous occurrence of living elements of these two organisms was proved by culture."

Atre, W. G., Wakankar, P. S. & Padhye, A. A. **Hamycin in the Treatment of Otomycosis (Preliminary Observations).** *Hindustan Antibiotics Bull.* Pimpri. 1961, May, v. 3, No. 4, 172–3.

The application twice a day with a swab of a 0·1% suspension of hamycin in glycerin was consistently successful in the treatment of 25 cases of external otomycosis, mostly due to *Aspergillus niger.* Recovery seems to have proceeded at a leisurely pace, all cultures being still positive on the 5th day of treatment, although usually negative on the 8th, and always by the 14th; there were no relapses in 2 months. *L. P. Garrod*

Berk, M., Fink, Grace I. & Uyeda, C. T. **Rhinomucormycosis. Report of a Case diagnosed by Clinical Signs.** *J. Amer. Med. Ass.* 1961, Aug. 19, v. 177, No. 7, 511–13, 5 figs.

"A fatal case of rhinomucormycosis, diagnosed clinically on the basis of characteristic physical signs in an uncontrolled, but nonketotic, diabetic, is presented. Cultures from the nasal exudate revealed *Rhizopus,* and tissue sections at necropsy disclosed hyphae. Amphotericin B was administered for 10 days during which time the

disease became progressively worse. The dosage was inadequate, however, and the disease too far advanced for proper evaluation of the drug. Mucormycosis should be tentatively diagnosed in a diabetic presenting with orbital cellulitis, proptosis, and ophthalmoplegia. Regulation of the diabetes and placement on amphotericin B therapy should be immediately undertaken before spread of the disease, and after nasal biopsy and cultures are taken."

YANG, Yen-Fei, HUANG, Rong-Fui & SHI, Man-Chien. **[Cephalosporium Keratitis]** *J. Formosan Med. Ass.* 1961, Mar. 28, v. 60, No. 3, 379–85, 4 figs. [11 refs.] [In Chinese.]

The English summary appended to the paper is as follows:—

"Two cases of hypopyon corneal ulcer, from each of which a species of cephaloporium fungus was cultured, are reported.

"These cases had been treated with cortico-steroids and were treated internally or topically with antibiotics, sulfa drug, antiseptic preparations and potassium iodide without any improvement.

"In the first case, the topical application of mystecline and nystatin appeared to influence favourably the healing of the corneal ulcer.

"Cephalosporium keratitis could be experimentally induced in traumatized mature rabbit corneas treated topically with steroids preparations by intracorneal inoculation of a saline spore suspension.

"We must pay attention to take care for steroid hormone locally used in the eye."

OHASHI, Y. **On a Rare Disease due to *Alternaria tenuis* Nees (Alternariasis).** *Tohoku J. Exper. Med.* 1960, Aug. 25, v. 72, No. 1, 78–82, 4 figs.

This brief account records a case of alternariasis due to *Alternaria tenuis* in a boy aged 11 years who complained of pollakiuria, haematuria and urodynia and who attended the Hanamaki hospital, Japan, as an outpatient. Repeated testing of the patient's urine consistently yielded conidia which were brown and ellipsoid and bore 1 septum terminally. They measured 10×5 microns. Cultures, when incubated at about 25°C., produced dark green colonies surrounded by a white fringe. These colonies developed conidiophores bearing catenulate conidia of *A. tenuis*.

Intraperitoneal inoculation of guineapigs with suspensions of the conidia obtained from the cultures resulted in 5 of 7 inoculated animals dying at 8 days after inoculation. Conidia were detected in urine samples obtained from them. Clinical abnormalities included oliguria and loss of weight. Post-mortem histological examination of the animals revealed conidia associated with an inflammatory reaction in the lungs, liver, kidneys and adrenal glands and they were also recovered from bile and urine samples withdrawn by puncture.

This fungus was totally inhibited by 30 units of trichomycin (Fujisawa Pharmaceutical Co. Ltd. Japan) per ml. *in vitro*; and guineapigs to whom this drug had been administered orally prior to being inoculated intraperitoneally with the conidia survived. The author found trichomycin to be also effective in several human cases of urinary infection with *A. tenuis*.

In addition, the author reports a total of 37 other cases of this infection in the neighbourhood of Hanamaki city which occurred within a period of 30 months. Conidia were observed in the cerebrospinal fluid of some of these patients.

The finding of conidia in the water of a well belonging to a family in which 3 members became infected suggested to the author that the soil and wells in the Hanamaki region are probably heavily contaminated by this fungus.

C. J. La Touche

Communicable Diseases

The order in this section is:—**Tuberculosis; Venereal Diseases; General Infective Diseases; Other Communicable Diseases.**

For the bacteriology of these diseases see the section on Bacteriology below. For diseases conventionally regarded as tropical, readers are referred to the TROPICAL DISEASES BULLETIN

TUBERCULOSIS

DUBOCZY, B. O. & BROWN, B. T. **Local Sensitization to Tuberculin.** *Amer. Rev. Respiratory Dis.* 1961, July, v. 84, No. 1, 69–77, 3 figs. [42 refs.]

Local sensitization to tuberculin which may be encountered in repeated tests at the same site can interfere with the specificity and reliability of the tuberculin test. The phenomenon has been reported by many workers, and some of the literature on the subject is reviewed by the authors in their introduction to the present paper.

Tuberculin reactions were studied in patients, employees and student nurses in a sanatorium in the United States from 1956 to 1959. It was found that an "early" reaction developed in the tuberculin-negative persons at the site of a previous test. This reaction differed from both the "immediate" and typical or delayed types. It is described as having sharply demarcated edges, elevated only a little, having diffuse redness and without vesiculation or necrosis of the skin.

In 3 groups of 18–35 student nurses this early reaction occurred in 76·0% on retesting in the same area with

10 TU of PPD and in 92·6% on retesting with 250 TU. Similar results were obtained in 100% in a group of 34 student nurses on retesting with 250 TU.

Details are given of the occurrence of a reaction within 3 hours in a nurse who had been tested with 1 TU and 250 TU twice yearly since 1954. She had never had a positive reaction. On the occasion described, in 1958 a test with 250 TU at the site of earlier tests produced the early reaction mentioned which reached its maximum at 24 hours and had almost completely disappeared at 48 hours. Such a reaction is not a positive tuberculin reaction. The phenomenon was also seen in a student vaccinated with BCG on retesting at the site of a test made 7 years earlier. It was not seen at the site of an old test made 23 years ago.

In reactors the early and delayed reactions are combined. The early reaction starts at 3–6 hours after injection reaches its maximum at 12 hours and usually decreases. In the meantime a delayed reaction develops and may persist for 7 days or may disappear earlier. In some persons with low-grade sensitivity the delayed reaction may not reach the positive range until the 5th day so that both the early and the delayed reactions can be seen separately. The early reaction starts in 3 to 6 hours and disappears within 48 hours; the delayed reaction starts only after 48 hours, reaches the positive ranges on the 4th or 5th days and lasts more than 7 days. Examples of these reactions with actual measurements observed are given. The practical conclusion reached is that in view of the possibility of false positive and false negative readings in a sensitized area it is necessary to use a new site for each tuberculin test. *H. G. Calwell*

DUTTA, J. C. **Fatal Reaction following PAS.** *J. Indian Med. Ass.* 1961, July 1, v. 37, No. 1, 30–31.

"A case of pulmonary tuberculosis was initially treated with streptomycin and PAS. After a few days the patient was getting mild reactions with PAS (temperature with chill only). Administration of PAS was stopped and the temperature became normal. PAS tried for the second time to see how it reacted resulted in a fatal reaction."

HOPPE, R. Einflüsse der neuzeitlichen Therapie auf die Wiederherstellung der Erwerbsfähigkeit des Tuberkulosekranken. **[The Influence of Modern Methods of Treatment on the Rehabilitation of Tuberculous Patients]** *Deut. med. Woch.* 1961, Aug. 18, v. 86, No. 33, 1546–54, 1575–6, 9 figs.

There is ample evidence that the modern treatment of tuberculosis has led to great improvement in the patient's chance of full recovery. The author has found support for the claim in the statistics of health insurance certification in the Rhineland showing that the percentage of insured persons certified fit for work after incapacity due to tuberculosis is very much higher than in 6 other important disease groups.

Persons suffering from chronic disease become more difficult to rehabilitate as they are older, and this problem will become more prominent in the future as far as tuberculosis is concerned.

During the period 1930–36 the peak of tuberculosis morbidity in insured workers occurred at 20–29 years with a steady decline at higher ages; in 1957–59 the peak continued after 29 to over 50 with only a small decline at 40–49. Analysis by age of some 4,000 patients in sanatoria in the period 1949–1959 also showed a decline in the number of patients aged 16–30 years with a corresponding increase in older patients. In 6,000 patients in the same period healing of cavities occurred in 67% at 16–30 years, 54% at 31–45, 39% at 48–60 and in only 18% over the age of 60. Rates of sputum conversion were 68%, 47%, 48% and 34% respectively. These figures show that the outcome is affected unfavourably by advancing age.

In order to assess (retrospectively) the prognosis in pulmonary tuberculosis the author selected by punch-card technique 648 patients out of 3,562 discharged from 5 sanatoria in 1957 and reviewed their state in 1960. There were 243 who had had active closed tuberculosis without cavitation and with negative sputum; 69% were at work, 26% were still incapacitated and 5% had died. There were 257 who had had open disease with cavitation in whom closure and sputum conversion had been achieved; 59% were at work, 38% were still ill and 3% had died. The third group consisted of 148 patients who had had open disease with cavitation which persisted and in whom the sputum had remained positive. Only 5% were at work, 71% were still incapacitated and 24% had died. None of these patients had undergone pulmonary resection or had had intrapleural pneumothorax induced, and at the time of their discharge there had been no prospect of their regaining fitness for work.

Most of those whose illness followed a favourable course were able to return to their previous occupation, and 51% of the patients with the least advanced disease (group 1) and 39% of those in group 2 were back at work within 6 months of discharge from the sanatorium. Care should be taken, however, that work is not resumed prematurely and that it is considered suitable by the physician. Failure to observe this safeguard entails risk of breakdown. *H. G. Calwell*

See also p. 1226, BRUNO **[Miniature X-Rays in Industry]**.

KENDIG, E. L., Jr. **Unclassified Mycobacteria in Children. Correlation of Skin Tests and Gastric Cultures.** *Amer. J. Dis. Children.* 1961, June, v. 101, No. 6, 749–55, 3 figs.

As it was noted that the tuberculous infection rate among patients attending the well baby clinic at the Medical College of Virginia was extremely high it was thought possible that some of the positive tuberculin reactions might be due to some cause other than infection with *Myco. tuberculosis*. 105 children were admitted to the study with a diagnosis of asymptomatic primary tuberculosis; the criteria for admission being similar to those set for the United States Public Health Service study on isoniazid as a prophylactic against tuberculous meningitis; thus all the children had a positive reaction in a Mantoux test. Approximately one half of the children admitted to the study were less than 3 years

of age; 4 were under 6 months of age, and 5 others less than 1 year old. 93 of the 105 were negro.

Gastric culture was positive for acid-fast bacilli in 17 patients but in only 8 of the 17 was *Myco. tuberculosis* isolated. In 5 cases the organism grown was a photochromogen, and in 4 a scotochromogen. 6 of the 8 cultures of *Myco. tuberculosis* were found to be virulent for guineapigs, and the other 2 were not tested. None of the photochromogens or scotochromogens was virulent for guineapigs.

In all 8 instances *Myco. tuberculosis* was shown to be sensitive to isoniazid. Of these, 7 were highly sensitive (0·1 μgm. per ml. of serum), and 1 was much less so (10 μgm.). Of the 4 photochromogens tested, 2 showed sensitivity to 1 μgm. per ml. serum, one to 5 μgm., and the other demonstrated partial resistance to 10 μgm. Results with the scotochromogens were similar, with 2 showing sensitivity to 1 μgm. per ml. serum, 1–5 μgm., and the other partially resistant to 10 μgm. In spite of the difference in sensitivity noted, gastric cultures at the completion of 12 months of isoniazid therapy were negative in all instances.

Attempts at correlation of skin tests and results of gastric culture were satisfactory in only 2 groups, the non-photochromogens and the *Myco. tuberculosis*. While infection with photochromogens and scotochromogens seemed widespread in this geographical area the resultant disease is probably rare, although it is possible that these mycobacteria may cause a positive tuberculin reaction.

F. H. Young

Brönnestam, R. **Two Cases of Pulmonary Disease due to Atypical Mycobacteria in South Sweden.** *Acta Tuberculosea Scandinavica.* 1961, v. 40, No. 3, 215–21. [14 refs.]

The first of these strains of atypical mycobacteria was isolated in 1959 from the sputum of a man, KH, aged 51 years. In 1954, after he had worked for 12 years at a refinery of an iron works, he developed a slowly progressive parenchymal lesion of the lungs. The disease did not respond to treatment with streptomycin, isoniazid and PAS, and in 1959 lobectomy was performed. The bacillus was recovered from the lesion by culture but not by guineapig inoculation.

The second strain was from a man, HB, aged 57 years. He died from cardiac failure in 1959 after an acute respiratory illness. The bacillus was isolated by cultivation, but not by guineapig inoculation, from the pulmonary lesions, which were histologically considered to be tuberculous. The patient had had a history of left-sided pneumonia in 1946, after which he had been troubled with shortness of breath.

Strain KH was a scotochromogen, its growth being orange and unaffected by exposure to light, and strain HB was a non-photochromogen, its growth being pale yellow. Both strains grew at 20°C. and scantily at 45°C.; growth was more rapid than that of the tubercle bacillus. Inoculation of 1 mgm. of both strains into guineapigs produced only local lesions, but large inocula produced lesions in the regional, lumbar and portal glands, and in the case of strain HB also in the spleen; neither strain was pathogenic to hens. Both strains were catalase positive but peroxidase negative, and they were resistant to streptomycin, isoniazid, PAS, viomycin and cycloserine.

S. R. M. Bushby

Bialkin, G., Pollak, Ann & Weil, A. J. **Pulmonary Infection with *Mycobacterium kansasii*.** *Amer. J. Dis. Children.* 1961, June, v. 101, No. 6, 739–48, 7 figs. [48 refs.]

The authors point out that atypical acid-fast organisms have frequently been shown to produce pulmonary disease in adults, but rarely in children. Adult pulmonary infection with atypical acid-fast organisms has been described with increasing frequency in the central United States, usually due to *Mycobacterium kansasii* (which is the name given to photochromogens) while along the southern Atlantic coast it is usually due to the Battey organism. The paper gives a classification of atypical mycobacteria pathogenic for human beings as described by Runyon. A short review is given of the cases reported in the literature in which disease in childhood was thought to be due to atypical mycobacteria.

The authors report 2 children in whom disease was apparently caused by the atypical mycobacteria. In both patients *Myco. kansasii* was recovered, but no typical tubercle bacilli were found although repeated searches were made.

A 4-year-old Puerto Rican girl presented with acute respiratory infection followed by persistent, intractable, spasmodic, productive cough and wheezing, with fever spiking to 102°F. X-ray showed consolidation of the right base; later, consolidation appeared at both bases. Sputum and gastric cultures obtained 9 days after admission were both positive for an acid-fast, photochromogenic, rod-shaped micro-organism. The skin test was negative to PPD. As the cultures were not available the patient was treated with chlortetracycline and the temperature gradually levelled off. The child was discharged and sent to Puerto Rico for convalescence; without further medical care she continued to improve and was reported by the mother to be apparently well 3 months later.

The second patient was a 10-year-old Puerto Rican girl admitted to hospital because of an unresolved pneumonia due to an atypical acid-fast organism. During the previous 8 years she was admitted to hospital on several occasions, at first as a case of primary tuberculosis. At the time of admission she was complaining of anorexia, weight loss, a cough, and fever, with daily spikes to 102°F. X-ray of the chest revealed a prominence in the left paratracheal region and in the upper pole of the left hilum which were, presumably, enlarged lymph nodes. They were accompanied by streak-like infiltration extending toward the subepicardial region and laterally. Sputum specimen grew a few golden yellow photochromogenic colonies of acid-fast bacilli. The Mantoux test was positive. The patient was treated with isoniazid and streptomycin. The follow-up X-ray showed definite progression in the lesion. Later the patient improved clinically but unfortunately she was sent back to Puerto Rico and no follow-up information was available.

A useful table showing the bacteriology of *Myco. kansasii* and the scotochromogens is given. An extensive bibliography is appended. *F. H. Young*

DAVIS, S. D. & COMSTOCK, G. W. **Mycobacterial Cervical Adenitis in Children.** *J. Pediatrics.* St. Louis. 1961, June, v. 58, No. 6, 771–8. [22 refs.]

Mycobacteria other than *Mycobacterium tuberculosis* can cause disease in man, and in order to obtain information concerning the aetiological importance of such atypical organisms the authors studied all available cases of mycobacterial cervical adenitis in children in Columbus, Georgia, U.S.A.

There were 24 cases which met the criteria of the study. All the children were Mantoux tested with 0·0001 mgm. of PPD-S, later also with PPD-B (from the Battey bacillus) and, from 1960, also with PPD-G (from a scotochromogenic mycobacterium isolated from one of the children).

Pus was obtained for examination from 17 children and examined in 14 cases; positive cultures were found in 11. Details of the techniques used and methods classifying the organisms are given. Where bacteriological diagnosis was not possible the pattern of skin sensitivity to the various tuberculins was the criterion of classification of the infecting organism.

No other cause of the adenitis was found in any of the 24 children; all nodes excised showed granulomatous changes on histological examination. 7 children were assigned to the tuberculous group (2 on bacteriological grounds and 5 because they showed larger or equal reactions to PPD-S than PPD-B or PPD-G. In only 1 of the 7 was the reaction to PPD-S clearly the largest. The bacteriological findings and the results of skin tests conflicted in 1 case but the bacteriological classification was regarded as the more convincing.

17 children were classified as having been infected by an atypical mycobacterium. Acid-fast bacilli were demonstrated in 10 of 13 attempts, once in a section of a gland and once in a culture reported as "positive for acid-fast bacilli" by another laboratory. The remaining 8 all showed small smooth colonies. The tuberculin tests supported the classification.

The tuberculous group differed from the other in that it contained the only 2 children with a history of prolonged household exposure to tuberculosis. The onset of the condition in all of the tuberculous children was associated with no other symptoms although 6 of them had lesions elsewhere. In 5 of the "atypical" group, however, the onset was accompanied by fever and evidence of upper respiratory infection; associated lesions were found in only 1 child. In other respects the groups were similar.

Almost all the children were treated, with no significant differences; 18 were operated upon (excision 8, incision and drainage 9, aspiration 1). Chemotherapy was given to 19. All were living and well at the time of reporting of whom 6 were still under treatment.

The results indicated that both surgical and medical treatment may be indicated in the condition. Excision gave better results than incision and drainage; it was followed by fewer draining sinuses and afforded the best specimens for bacteriological examination. Chemotherapy also appeared to reduce the risk of a draining sinus. "In the future, as infection with *Myco. tuberculosis* continues to diminish, atypical myco-bacteria will undoubtedly be responsible for an increasing proportion of cases of chronic cervical adenitis." *H. G. Calwell*

VENEREAL DISEASES

BROWN, W. J. **Cluster Testing—a New Development in Syphilis Case Finding.** *Amer. J. Pub. Health.* 1961, July, v. 51, No. 7, 1043–8.

Cluster testing is simply an extension of contact tracing in an effort to bring in as many persons suffering from venereal disease, mainly syphilis, as possible with the minimum of effort.

This article starts with the story of a young man travelling away from home whose father telephoned him to say that his girl friend had syphilis [how the father got to know is not clear]; this young man was 1 of 35 who had had sexual relations with the same girl during the same evening [so presumably quite a few cases of syphilis were found].

After setting out the general principles of venereal disease control such as education and information, selective blood testing and contact tracing, the author explains that "cluster" includes "suspects" *i.e.* persons possibly needing blood tests and "associates" *i.e.* persons named by or found in the company of sex contacts "or suspects". This is followed by a debate between a visitor [presumably a social worker] and 4 other named persons [who and what they were is not clear]. This debate ranges over a wide field and tells how various persons suffering from syphilis were found by indirect methods [though it is not always easy to follow as Christian and surnames are used indifferently]. What emerges is that every new case of infectious syphilis is the beginning of a "cluster" which ends when all leads from the first contact to the last suspect or associate have been tested. The average cluster ranges from 25 to 30; when several members of a cluster lead to a particular place, *e.g.* bar or "hang-out", all who frequent it should be persuaded to have blood tests. The successful cluster investigator must be prepared to "talk his head off" and work "like the very devil". *T. E. Osmond*

FUCHS, G. H. P. Die statistischen Wahrscheinlichkeiten der Spirochaetales-Eiweissreaktion (Pallida-Reaktion nach Gaehtgens und Fühner). Vergleichende Studien zu den Ergebnissen des TPI-Testes und der Cardiolipin-Kolmer-Reaktion bei sicherer Lues verschiedener Stadien und luesfreien Personen. **[Statistical Probability of the Spirochaetal Protein Test (Pallida-Reaction according to Gaehtgens and Fühner). Comparative Study of Results of TPI (Nelson) Tests and Kolmer Cardiolipin Tests in Cases of Ascertained Syphilis of Different Stages and in Non-Luetics]** *Ztschr. f. Immunitätsf. u. Exper. Therap.* 1961, v. 121, No. 5, 395–419. [218 refs.]

The English summary appended to the paper is as follows:—

"In view of the present inadequate serologic diagnosis of syphilis, the spirochaetal protein reaction (Pallida reaction) basing on an antigen of Reiter spirochaetes represents a useful supplement to the commonly used diagnostic procedures with the aim of widening the 'serologic general aspect'.

"This was recognized by studying a selected group of 644 individuals whose sera were tested for spirochaetal protein antibodies comparing the results with those of the corresponding TPI tests and the most commonly used standard serologic reactions.

"20 non-luetics of 331 (TPI negative) were found to be positive with the spirochaetal protein reaction; this represents a specificity of 94·0 per cent. On the other hand only 139 luetics of different stages of a total of 313 showed spirochaetal protein antibodies corresponding to a recovery rate ('sensitivity') of 44·4 per cent.

"Considering this unsatisfactory defection rate, the exclusive use of the spirochaetal protein reaction—just as that of other immunobiological methods—is not to be recommended in spite of several advantages [good probability of detection (87·4 per cent), small coefficient of non-specificity (6·0 per cent), high proportion of isolate positive results (7 patients of 313)]. Only in addition to lipoid fixation reactions the spirochaetal protein reaction increases the completeness of the 'serologic general aspect' and contributes to the reliability of diagnostic procedures."

COLLOMB, H., DIOP, M. & VANIER, G. La syphilis du système nerveux en milieu africain. **[Neurosyphilis in Africans]** *Méd. Afrique Noire.* Dakar. 1961, June 16–30, v. 8, No. 12, 250–51.

The incidence of neurosyphilis in Africans has been variously assessed. These authors found 29 cases in 22 months among 1,600 patients attending a neuro-psychiatric clinic at Dakar; these included 2 of myelitis, 3 of cerebral arteritis and 24 of general paralysis (G.P.I.): only 1 case of cerebral gumma was seen and no case of tabes; the average age was 46; 26 were males and 3 were females.

In GPI the onset is difficult to decide; usually there is a long history of mental trouble (50%) but in 7 cases it was only a matter of months or even weeks. Neurological signs include headache, tremors, dysarthria, difficulty in walking with perhaps hemiplegia or epilepsy; Argyll-Robertson pupils were found in only 3 cases. Psychological troubles were very variable, including confusion, hallucinations, delirium, melancholia, etc., but delusions of grandeur were only found in 3 cases; most patients showed changes in encephalograms. Blood and cerebro-spinal fluid reactions were typical. Diagnosis was usually easy but trypanosomiasis had to be excluded since it may give rise to false positive serum reactions. Of the 24 patients 6 died, 2 remained stationary, 8 showed improvement and 8 were "cured".

Therapy included general anti-inflammatory and specific measures; first it is very important to improve the general condition of the patient (rehydration, plasma, transfusion and vitamins); cortisone in fairly large doses at first can be followed by specific drugs. Doses of penicillin should not exceed 20,000–50,000 units for the first few days; stovarsol and bismuth were tried occasionally but their value was difficult to assess [no doubt it was negligible]. Malaria therapy is useless in the African.

T. E. Osmond

LUNN, H. F. **Treponematosis of Bone. A Case for Discussion.** *J. Trop. Med. & Hyg.* 1961, July, v. 64, No. 7, 166–8, 2 figs.

The case described here is of a man, belonging to the Acholi tribe, Uganda, aged 24, who gave a history of a limp and pain in the right thigh for the previous 8 months. On examination the right thigh was 4 cm. bigger in diameter than the left and the right lower limb was 2 cm. shorter than the left; abduction and adduction were limited and there was fixed flexion of 20° of the right hip; there was generalized lymphadenopathy but no other signs of syphilis or yaws except a positive Kahn reaction. A radiogram showed necrosis of the head of the right femur, the shaft showed a deposit of subperiosteal new bone and irregular osteolytic areas, and these changes indicated chronic osteomyelitis with extension into the hip joint; minor changes were also seen in the left femur. Biopsy of a piece of bone and material from the medullary cavity showed infiltration with plasma cells and lymphocytes, and dark-ground examination revealed organisms indistinguishable from *Treponema pallidum*. Treatment consisted of 3 courses each of 15 mega units of soluble penicillin given over 15 days and 0·2 gm. bismuth weekly for 10 weeks.

Within 2 months the patient was walking well with a calliper, and pain was much less; 18 months later he could walk 2 miles without aid, shortening had increased to 4 cm. but movements at the hip joint were freer and less painful.

It is suggested that the lesions were due to late or relapsing secondary syphilis [or yaws] progressing to gummatous changes. *T. E. Osmond*

BRITISH J. VENEREAL DIS. 1961, June, v. 37, No. 2, 89–186, numerous figs. [Numerous refs.] **Gonorrhoea and Non-Gonococcal Genito-Urinary Infections. A Symposium organized by the International Union against the Venereal Diseases and the Treponematoses and the Polish Society for Dermatology and Venereology held at Cracow, Poland, in September, 1960.**

At a symposium organized by the International Union against the Venereal Diseases and the Treponematoses (IUVDT) and the Polish Society for Dermatology and Venerology held at Cracow, Poland, in September 1960, the following papers were read.

A. J. KING and C. S. NICOL (pp. 92–99) spoke of *The Problem of Gonorrhoea with special reference to England and Wales* and showed that its incidence had steadily increased since 1955. In turn they dealt with prevention, laboratory methods, clinical aspects and treatment; stress was laid on the frequency of reinfection, homosexuality and on the reservoir of infection in women with latent disease.

Epidemiology and Control of Gonorrhoea in Poland were dealt with by T. Z. CAPINSKI and J. BACHURZEWSKI (pp. 100–106); they gave a number of statistics shown in 13 tables which indicate that the disease is not increasing in Poland but its importance must not be underestimated; prostitution plays a large part as does alcohol, but teenagers do not present a special problem.

P. DUREL spoke of *Gonorrhoea and Non-gonococcal Infections* (NGU) in France (pp. 107–114). Gonorrhoea incidence is fairly steady but NGU is a serious problem; treatment relies mainly on streptomycin but a combination of this with spiramycin seems desirable; susceptibility of strains of gonococci to antibiotics demands much research; teenagers do not present a serious problem in France.

A. PERDRUP spoke of *Gonorrhoea in Denmark* (pp. 115–119) and showed that Copenhagen provides most cases (statistics from 1870–1959 are set out in a table); fluctuations in incidence are largely associated with historical data; the abolition of brothels in 1901 and that of the regulations for prostitutes in 1907 was followed by a large increase in the incidence of the disease.

In *Gonorrhoea and its Control in Finland*, A. S. HÄRÖ (pp. 120–125) states that a slight increase occurred in 1959; travel and tourism are largely held responsible; young males are increasingly being infected, Helsinki accounts for nearly half the total cases, and restaurants are the commonest sources of infection. International standards of laboratory and treatment methods are desirable.

G. TASSI recounts the *Present Situation of Gonorrhoea in Italy* (pp. 126–127). The incidence of gonorrhoea is stable but syphilis is increasing; dosages of penicillin for the former vary from 1·5 to 3 mega units; control is hampered by increase in promiscuity, emancipation of the sexes and tendency to prostitution among modern women.

Campaign Against Gonorrhoea in Hungary by I. KÁROLYI, F. FÖLDVÁRI, and L. KOVÁCS (pp. 128–129) shows that gonorrhoea seems to be decreasing in Hungary; it is essentially an urban rather than a rural disease; the male : female ratio is 2 : 1 in acute cases but 1 : 3 in chronic ones. Treatment is compulsory and free, brothels have been closed and prostitutes rehabilitated.

M. CARDIA and A. DA FONSECA deal with the *Epidemiological Aspects of Gonorrhoea in Oporto, Portugal* (pp. 130–131). The incidence of gonorrhoea remains at a steady high level; the disease accounted for 10·2% of all patients reporting at the Dermatological and Gynaecological Dispensary in 1959 compared with 6·3% in 1958. Latent cases need detection.

The *Epidemiology of Gonorrhoea in Bulgaria* is presented by P. BOTZOV (pp. 132–134). The incidence is low and decreasing; most cases occur in July-August and in persons aged 21–30; the disease is essentially urban and is compulsorily notifiable; contact tracing is successful in 60%.

Urethro-Genital Gonococcal Suppurations observed during the past 3 years in the Charles Nicolle Hospital, Tunis by A. KHALFAT (pp. 135–137) shows that gonorrhoea is decreasing though complications are relatively common; treatment usually consists of 1·2 mega units of penicillin; brothels and prostitutes are declining.

I. S. NIELSEN considers *Gonorrhoea in Teenagers* (pp. 138–141) in Denmark and more especially in Copenhagen. The incidence of gonorrhoea in females aged 15–19 rose steadily from 1944 to 1960 (854 to 1,384 cases) but, incidentally, the rise was not nearly so great as in Sweden. 40·8% of female gonorrhoea was found at age 15–19 years, 34·9% at 20–24 and 13·6% at 25–29.

B. MICHAŁOWSKI recounts the *Difficulties in Diagnosis and Treatment of Gonorrhoea in Young Girls* (pp. 142–144) in Poland, both social and medical. The number of cases reported from 1950–1959 varied from 68 to 184 in those up to 3 years of age and from 56 to 307 in those from 4–14. The author thinks vulvo-vaginitis too narrow a term, cervix and urethra often being involved. Hormones, penicillin and streptomycin are the best forms of treatment.

Alice REYN contributes a very long and detailed article on *Sensitivity of N. gonorrhoeae to Antibiotics* (pp. 145–157) with 10 figures and 1 table. 950 strains were tested against penicillin, streptomycin, tetracycline and sulphathiazole. Less sensitive strains to penicillin seem to be appearing and clinical and pathological sensitivity seem to run parallel; some strains seem almost completely resistant to streptomycin but tetracycline seems to retain its effectiveness; in 1954 the sensitivity level against sulphonamides was about the same as that "before the sulphonamides were introduced into therapy" [whatever that may mean].

E. H. LETCHNER and C. S. NICOL write of *A Comparison of Sensitivity to Penicillin of N. gonorrhoeae 1960 and 1958* (pp. 158–160): of 107 strains in 1960, 91% were sensitive and 9% [relatively] insensitive; recurrence rate was 13% where sensitive strains were concerned against 38% with insensitive ones. Relative resistance *in vitro* fell from 19% in 1950 to 10% in 1960; this was probably due to the higher dosage of penicillin in the latter year.

F. J. G. JEFFERISS and N. ROSEDALE report results of *Treatment of Gonorrhoea with Phenethicillin (Broxil)* (pp. 161–163) with 1,000 mgm. of this drug given orally in 2 doses; the failure rate was 12% compared with 6·5% after 600,000 units of procaine penicillin given as a single injection. They conclude that oral therapy is unsatisfactory unless the patient can be relied on to follow instructions.

K. LEJMAN and J. BOGDASZEWSKA-CZABANOWSKA give their *Clinical and Microbiological Observations on Non-gonococcal Infections of the Male and Female Genito-Urinary Tract* (pp. 164–169); bacterial, monilial and trichomonal discharges are the commonest in women; in 162 men suffering from non-gonococcal urethritis 20 were

found to harbour *Trichomonas vaginalis*. Excellent photographs show monilia and aberrant forms of *T. vaginalis*, some of which are engulfed by leucocytes.

M. Cardia deals with *Non-gonococcal Vaginitis* (pp. 170–171) in Oporto. Of 10,547 [female] patients seen in 1954–1958 4,202 had VD (572 syphilis, 485 gonorrhoea, 71 soft chancre, 2 lymphogranuloma venereum and 3,072 trichomoniasis); Trithéon proved very effective for this last.

B. Hoffmann, W. Kilczewski and E. Małyszko report *Studies on Trichomoniasis in Males* (pp. 172–175) [and also in females]. For diagnosis cultures were more successful than smears; the organism was found in 7% of males and more often after treatment for gonorrhoea than before; the most common site in males was the semen.

P. Popchristov and V. Berov report results of *Treatment of Trichomonal Vaginitis and Urethritis and Their Complications with Metronidazole ("Flagyl")*; (pp. 176–178). They stated that trichomoniasis is "as common in men as in women"; treatment consisted of 0·25 gm. twice daily for 10 days for males and a 0·5 gm. tablet per vaginam daily for 10–20 days in females; side effects were seen in 9 of 22 patients but were mostly mild; no serious blood changes were seen.

C. Plácido de Sousa and F. N. Brandão discuss *Epidemiological Aspects of Lymphogranuloma Venereum* (pp. 179–182), a study of a group of prostitutes. Complement-fixing antibodies were found in 60% of 50 prostitutes (in 81% of the older and in 35% of the younger ones); in 24 cases those against *Bacterium anitratum* were also present. The Frei test was positive in 10 out of 32 cases but was only positive half as often as the complement-fixation test.

The final article, by J. Horoszewicz is on the *Incidence of Pleuro-Pneumonia-Like Organisms (P.P.L.O.) in Man* [? in human beings] (pp. 183–186). These were cultured from 1,121 persons including 297 women and skin reactions were observed in 90 persons; of 519 females 302 showed PPLO (58·2%); the corresponding figures for males were 268 and 102; semen was a common site. Intradermal tests were positive in 54 out of 90 cases. PPLO were isolated from the oral cavity of 179 out of 334 persons, most of them healthy. *T. E. Osmond*

Allison, J. R., Jr. **Demethylchlortetracycline Hydrochloride in the Treatment of 267 Patients with Acute Gonorrhea: Results and Evaluation.** *Antibiotics & Chemotherapy*. New York. 1961, July, v. 11, No. 7, 454–60, 1 fig. [17 refs.]

The ideal drug for the treatment of gonorrhoea should (1) be effective in a single dose, (2) quickly achieve bactericidal blood levels, and (3) be free from side effects.

This author treated 267 patients (227 males and 40 females) suffering from gonorrhoea with demethylchlortetracycline according to 2 schedules; 123 received a single dose of 600 mgm., and 144 a dose of 900 mgm., by mouth, and patients were instructed to return after 1 week. 249 patients were coloured and 18 white; no less than 116 were aged 11–20 years.

The apparent cure rate with the lower dosage was 84% and with the higher dosage 93%; side effects were 21% with the former and 40% with the latter. Parenthetically, the author ascribes the relatively high incidence of side effects in his series to (1) larger single doses, (2) poor nutritional state of his patients, and (3) very close questioning concerning reactions.

Side effects were mostly gastro-intestinal (nausea 38, vomiting 20, diarrhoea 7, loose stools 15, dizziness 7 and headache 2); no anaphylactic or skin reactions were seen. Symptoms [? signs] disappeared in 1 day in 81 patients, in 2 days in 54 and in 3 days in 29.

Blood levels were adequate for at least 48 hours after either dosage, but there were considerable fluctuations.

[It would be interesting to know the respective cure rates in males and females and in coloured and white patients.] *T. E. Osmond*

Ziprkowski, I., Krakowski, A. & Roubenoff, D. **[The Sensitivity of Gonococci to Penicillin and Kanamycin in Israel]** *Harefuah*. Jerusalem. 1961, Aug. 15, v. 61, No. 4, [in Hebrew 121–3. (16 refs.) English summary 123].

The English summary appended to the paper is as follows:—

"A hundred men suffering from acute gonorrheal anterior urethritis were treated during the period 6.1.59 to 1.10.60. The sources of infection of these patients were dispersed throughout the country and thus it can be presumed that the gonococci isolated represented a cross-section of the gonococcal population in Israel.

"Ninety-one patients were treated with penicillin and cured although 2 patients continued to have an urethral discharge, but no further gonococci could be demonstrated. In 5 patients gonorrhea again occurred some time after healing, but reinfection was most probable in all of these. Nine patients were treated with kanamycin and all were cured.

"The good results in the penicillin treated patients might suggest that the gonococci in Israel are more sensitive to penicillin than foreign strains. In order to elucidate this problem sensitivity tests were performed on 28 *Neisseria gonorrheae* strains isolated in pure culture. Dilutions of 0.01 u/cc of penicillin and partly of 0.05 u/cc did not inhibit the growth of gonococci. Some years ago bacteriostasis was adequately demonstrated with these same dilutions. Thus it can be concluded that the sensitivity of gonococci to penicillin in Israel has actually diminished. On the other hand, all the 28 cultures were inhibited by 0.1 u/cc of penicillin. The homogeneity of these results indicates absence of penicillin-resistant mutants.

"In the light of these facts, the clinical success in the treatment of gonorrhea can be attributed to the high dosage of penicillin administered—1,000,000 U per day, on each of 3 successive days. In the authors' opinion this dosage is indicated and at present is sufficient to heal acute gonorrheal anterior urethritis in men and thus should be recommended as standard treatment.

"The kanamycin treated patients (0.5 gm. kanamycin i.m. twice daily, on 3 successive days) were all cured. The sensitivity test gave homogeneous results—bacteriostasis was obtained with 0.1 mcg/cc of kanamycin. These

results were in accordance with the expectation, since this antibiotic has not yet been utilized in the treatment of gonorrhea."

SCHWIMMER, B., HENDERSON, N. D. & OLSON, B. H. **Treatment of Acute Gonorrhea in Males with Synnematin B.** *Pub. Health Rep.* Wash. 1961, July, v. 76, No. 7, 630–32.

This antibiotic [this *Bulletin*, 1960 v. 35, 569] has been shown to be related to penicillin; it is spirochaetocidal and gonococcocidal and is of very low toxicity.

These authors treated 132 males suffering from acute gonorrhoea with a single injection of 300,000 units; 112 were presumably cured (clinically free and with negative smears and cultures 8 or more days after treatment) and 20 showed a discharge within 30 days; of these latter 3 showed negative and 17 positive smears and cultures. Of the 17, 11 were considered reinfections, 5 were failures and 1 was considered successful (being negative at the 3rd visit without further treatment). In comparison 100 unselected similar patients were treated with 1·2 mega units of PAM; 92 were cured, 7 were considered reinfections and 1 a treatment failure.

T. E. Osmond

ČERVA, L. & ČERVOVÁ, Helena. Výskyt *Trichomonas intestinalis* u žen a souvislost této nákazy s vaginální trichomonazi. **[Occurrence of *Trichomonas intestinalis* in Women and Connexion of the Infection with Vaginal Trichomoniasis]** *Československ. Epidemiol., Mikrobiol., Imunol.* Prague. 1961, v. 10, No. 2, 128–33, 2 figs. [29 refs.] English summary.

609 women aged from 15 to 65 years were examined in 1958–59 in the central hygiene and epidemiological station in Prague for the presence of infection with *Trichomonas vaginalis* and *T. intestinalis* [presumably *T. hominis*]. Vaginal secretion was examined microscopically in stained smears and was also cultured on Vf broth with 10% rabbit serum and antibiotics, and samples of stools were inoculated on egg medium layered with Locke solution and 10% sheep serum. *T. vaginalis* was isolated from 151 women, most frequently in the 40–49 year age-group. *T. intestinalis* was isolated from only 2 women, aged 37 and 44 years. The results obtained thus showed no relationship between the occurrence of infections with the 2 species of *Trichomonas*. Among other protozoa *Entamoeba coli* was found in 7, *E. histolytica* in 2, *Endolimax nana* in 9 and *Iodamoeba bütschlii* in 1 woman.

D. J. Bauer

PETRU, M. Studie o urogenitální trichomoniáze. I. Pokus o standardizaci kultivační diagnostiky a její význam. **[Study of Urogenital Trichomoniasis. I. An Attempt to Standardize Cultivation Diagnosis and its Significance]** *Československ. Epidemiol., Mikrobiol., Imunol.* Prague. 1961, v. 10, No. 2, 124–7. English summary.

The author has developed a method of storage of Johnson medium for the cultivation of *Trichomonas vaginalis*. The freshly prepared medium is placed in transfusion bottles which are then steamed for one hour, during which time they are exhausted of air through a needle passed through the rubber bung. The needle is removed while the bottles are still hot, and they are subjected to further sterilization on the next 2 days. The bottles are then stored in the evacuated state at 2°C. Before use 10% sheep serum and penicillin are added and the medium is distributed into tubes for immediate use. In the examination of 849 women *T. vaginalis* was isolated in 178 instances (21%) when freshly prepared medium was used, and in 72 of 336 (21·5%) instances when medium stored for 3 months was used.

D. J. Bauer

GENERAL INFECTIVE DISEASES

The order in this section is:—**General; Hospital and other Cross Infections; Coccal Infections; Bacterial Infections; Virus Infections.**

GENERAL

PROC. ROY. SOC. MED. 1961, Mar., v. 54, No. 3, 181–9 (Sect. Gen. Pract. 1–9), 4 figs. [Numerous refs.] **Discussion on Infectious Diseases Today** [WATSON, G. I.; LEFF, S.; STUART-HARRIS, C. H.]

Among the many points raised in this discussion the following, from Professor Stuart-Harris, seem of particular interest. Virus isolation, although not conclusive as to causation, is the best method of diagnosis in diseases associated with many of the new-found viruses of the alimentary and respiratory tracts; serological evidence may be difficult to obtain because of the multiplicity of antigenic viral types [there are now 19 known types of coxsackie and 29 of ECHO viruses]. In the adenovirus group, however, there are common complement-fixation antigens, and this simple test is generally applicable. For other viruses neutralization tests in tissue cultures with acute and convalescent sera may have to be applied, or other techniques used. The evidence for an antigenic relationship of the measles and dog distemper viruses is still conflicting. Enders's living attenuated measles virus produces immunity at the expense of producing a modified measles similar to that obtainable with prophylactic gamma globulin. This protection is nevertheless desirable in view of the respiratory and occasional encephalitic complications of measles. The well-known clinical

syndrome of roseola infantum has now been shown to be due to enteroviruses, and in epidemic form has in recent years been associated with abacterial meningitis and with ECHO 9 virus. The form of atypical pneumonia associated with cold red cell agglutinins is now known to be due to Eaton's agent, and other forms to adeno- and other viruses. Croup in childhood appears to be often due to one or other of the parainfluenza viruses. The most interesting recent discovery in the field is the growth of several viruses of the common cold in tissue culture—at a temperature of 33°C. and in specially acidified media.

Many interesting observations in the spheres of general practice and public health were made by the other speakers. *H. S. Banks*

PHILIP, C. B. **Arthropod Vectors in relation to the Reservoir Mechanism of Microbial Agents of Animal Diseases.** *Acta Tropica.* Basle. 1961, v. 18, No. 3, 257–62. [37 refs.]

HOSPITAL AND OTHER CROSS INFECTIONS

POWELL, D. E. B. **Staphylococcal Septicaemia in a General Hospital.** *Brit. Med. J.* 1961, Aug. 5, 336–9, 2 figs. [25 refs.]

The author traced 49 cases of staphylococcal septicaemia treated in a 360-bed hospital between 1950 and 1958: 40 of the patients died. Of the 49, 33 patients were admitted with the disease, 16 were infected after admission to hospital for treatment of another condition. Surgery and corticosteriod therapy were the two most important factors when infection occurred after admission. Renal disturbance was of great importance in prognosis—of 11 patients whose blood urea rose to over 100 mgm. % none recovered. Staphylococcal septicaemia occurring after admission to hospital has become or is becoming as lethal a condition as in the pre-antibiotic era. *A. B. Christie*

STOPPELMAN, Marie R. H. **The Occurrence of Infections with Antibiotic-Resistant Staphylococci in the Children's Hospital of the University of Amsterdam.** *Quart. Rev. Pediatrics.* New York. 1959, Jan.–Mar., v. 14, No. 1, 26–33. [21 refs.]

This paper concerns staphylococci from nose and throat swabs from all patients admitted to this hospital during 1955, and from lesions in patients during 1950–58.

These strains were tested for antibiotic sensitivity and phage typed. Strains resistant to penicillin and tetracycline were much commoner in patients who had had previous antibiotic treatment: this applied to both carrier and lesion strains. Evidence is presented that little cross-infection takes place in this hospital [this and other observations are difficult to interpret without much more information about the hospital itself, its clinical material, and the precautions perhaps contributory to this result]. The most striking individual observation reported is that out of 31 strains from patients admitted with pneumonia or empyema and untreated with antibiotics, only 3 were penicillin-resistant and 2 of these may have been acquired in the hospital in which the infant was born. "This low rate of resistant strains may reflect the relatively restricted use of antibiotics in general practice in Holland." *L. P. Garrod*

JÄRVINEN, K. A. J., KAHANPÄÄ, A., RANTASALO, I. & FORTELIUS, P. **The Incidence of Hospital Strains of *Staphylococcus aureus* in the Lungs of Patients who died in the Medical Department.** *Acta Med. Scandinavica.* 1961, July, v. 170, No. 1, 43–50. [10 refs.]

Bacteriological examination was made at autopsy of 76 patients dying in a medical department in Helsinki. *Staphylococcus aureus* was isolated from the lungs of 34 (45%) of the patients. Only 14 of the strains were typeable by phage and no one type was dominant. 12 strains, all untypable, were antibiotic resistant. 11 of 20 patients having histological evidence of pneumonia yielded staphylococci, compared with 18 of 44 with no such evidence. Staphylococci were isolated with greater frequency from the older patients, those who had been longer in hospital, and those who had been unconscious for a period before death. *R. E. O. Williams*

HENDERSON, R. J. & WILLIAMS, R. E. O. **Nasal Disinfection in Prevention of Post-Operative Staphylococcal Infection of Wounds.** *Brit. Med. J.* 1961, Aug. 5, 330–33.

Men and women admitted to the surgical wards of 2 hospitals were treated from the time of admission or shortly afterwards either with a neomycin-chlorhexidine cream (Naseptin), or with an inert cream, inserted into the anterior nares 4 times a day. The selection of the treated patients was by their hospital number, and the nature of the creams was not revealed to the ward staff. 420 patients had Naseptin treatment and 413 served as controls.

The Naseptin treatment appeared to control the nasal carrier state, for 82% of the treated patients became or remained non-carriers compared with 54% of the controls; 12% of the treated and 29% of the controls acquired a staphylococcus in the ward. However, the incidence of post-operative sepsis due to *Staph. aureus* was 5·0% in the treated and 4·6% in the control group; the incidence of symptomless *Staph. aureus* infection was 7·8 and 10·8% in the 2 groups respectively. This was somewhat surprising since, in the controls, the incidence of sepsis was much lower among the non-carriers (1·8%) than it was among the carriers (7·8%).

In discussion it is suggested that this apparent anomaly might be due to continued carriage by the treated patients in some undetected region, or by the fact that in the controls the wounds were not infected from the nose, but that both nose and wound were infected by some common source. It is also noted that in contrast to the work of GILLESPIE *et al.* [*cf.* this *Bulletin*, 1960, v. 35, 261]

less than half the patients present in the ward at any one time were under treatment. *R. E. O. Williams*

See also p. 1294, MACCABE *et al.*, **Erythromycin-Resistant *Staphylococcus aureus*.**

COCCAL INFECTIONS

The order in this section is:—***Staphylococcus, Streptococcus, Neisseria, others.***

MUNCH-PETERSEN, E. **Staphylococcal Carriage in Man. An Attempt at a Quantitative Survey.** *Bull. World Health Organization.* Geneva. 1961, v. 24, No. 6, 761–9, 2 figs. [Numerous refs.]

The author has surveyed the published records of surveys of staphylococcus carriage in adult populations since 1937 and summarized them all in a single diagram which shows that there has been no substantial change over the years, with the exception of an apparent sharp drop in the hospital population in 1949. [This diagram seems, however, of very limited significance since the points for each year are based on various numbers of reports, from different parts of the world, with varying cultural methods and apparently containing varying proportions of nose, skin, throat, wound, milk, etc. cultures.] A similar diagram based simply on nasal cultures also shows no secular trend. The paper concludes with discursive comments on a number of technical points involved in determining staphylococcus carriage.

R. E. O. Williams

DE HAAS, P. K. & FLU, F. P. Epidemiologisch onderzoek naar aanleiding van een nephritis-epidemie in Midden-Zeeland. **[An Epidemiological Study of a Nephritis Epidemic in Central Zeeland]** *Nederl. Tijdschr. v. Geneesk.* 1961, July 15, v. 105, No. 28, 1369–71. English summary (4 lines).

In an investigation of the prevalence of streptococcal infection and 22 associated cases of acute glomerulonephritis, 17 were attributed to Type 14 and 5 to Type 12 group A streptococci.

Investigation of schoolchildren and family contacts included throat swabs, sputum cultures, antistreptolysin titre estimations and urine tests.

In a town closely related to the town where infection was prevalent 115 positive swabs (throat) were found in 290 schoolchildren. The positives were reduced to 63 after 3 weeks this being attributed to the use of penicillin V.

In a comparable unrelated town 222 children gave 74 positives which remained much the same (73) after three weeks. In this town too, the absence of Type 14 was associated with fewer cases of nephritis.

The commonest streptococci types found were 3, 4/26, 12, 14. In patients with nephritis and their family contacts group A streptococci were isolated 17 times and Type 14 found 12 times.

[A very useful epidemiological investigation.]

K. Schwarz

JENNINGS, R. B. & EARLE, D. P. **Post-Streptococcal Glomerulonephritis: Histopathologic and Clinical Studies of the Acute, Subsiding Acute and Early Chronic Latent Phases.** *J. Clin. Investigation.* 1961, Aug., v. 40, No. 8, Pt. 2, 1525–95, 2 charts, 1 diagram & 71 figs. (6 coloured). [67 refs.]

WELCH, C. C., TOMBRIDGE, T. L., BAKER, W. J. & KINNEY, R. J. **Beta-Hemolytic Streptococcal Pneumonia: Report of an Outbreak in a Military Population.** *Amer. J. Med. Sci.* 1961, Aug., v. 242, No. 2, 157–65, 8 figs. [10 refs.]

The authors report 20 cases of beta-haemolytic-streptococcal pneumonia occurring in young men in a training centre in Illinois. The onset was abrupt, with no evidence of preceding viral infection except in 2 cases; the patients rapidly became acutely ill with dyspnoea, pleuritic pain and fever common to all. Streptococci were cultured from the throat in 14 patients, from the sputum in 13, from pleural fluid in 6 and from the blood in 1. One patient aged 17 died and post-mortem findings are reported. Penicillin was the antibiotic of choice but was given alone in only 8 cases: other antibiotics were given while cultures were pending because of the severe clinical picture. *A. B. Christie*

HORTON, G. E., GOURLEY, R. D., WALKER, R. H. & ULRICH, Elizabeth. **Current Observations in Pneumococcal Pneumonia: I. Azotemia as a Prognostic Omen.** *Amer. J. Med. Sci.* 1961, Mar., v. 241, No. 3, 322–8, 1 fig. [24 refs.]

This is a study of the blood urea nitrogen (BUN) in 103 patients with pneumococcal pneumonia, of whom 96 survived and 7 died. Those who survived either had a normal BUN or, if the BUN was elevated on admission, it declined to 25 mgm. per 100 ml. or less. Those who died of the pneumonia uncomplicated by other bacterial infections or by meningitis, had a BUN that was elevated and usually remained elevated. Consideration of the kidney pathology led clearly to the view that the azotaemia was non-specific and probably extrarenal in origin.

As a factor in prognosis of pneumococcal pneumonia, persisting and increasing azotaemia should be placed in a list of adverse conditions such as old age, infancy, late treatment, type III infection, multilobar involvement, leucopenia, bacteriaemia, jaundice, other complications *e.g.* cardiac and pulmonary disease and alcoholism.

H. S. Banks

OSWALD, N. C., SIMON, G. & SHOOTER, R. A. **Pneumonia in Hospital Practice.** *Brit. J. Dis. Chest.* 1961, July, v. 55, No. 3, 109–18.

The authors reviewed the records of 1,330 patients treated for pneumonia in St. Bartholomew's Hospital, London, between 1949 and 1958: 303 patients were under 15 years old, 277 were over 65. There were 109 deaths (8·2%), 98 in adults 11 in children. Of the adults who

died 59% were over 65 and 35% were moribund on admission. Pre-existing chronic bronchitis was present in 38% of the adults and in 52% of the patients who died. The main factors adversely affecting the prognosis in pneumonia were old age, pre-existing disease, especially chronic bronchitis, and inadequate or delayed treatment.

The pneumococcus was the commonest pathogen, but *Haemophilus influenzae* was also common in patients with associated respiratory diseases. *A. B. Christie*

BEECKMANS, G. Étude comparative de cent et onze cas de méningites purulentes chez l'enfant au Congo. [**Comparative Study of 111 Cases of Purulent Meningitis in Children in the Congo**] *Ann. Soc. Belge de Méd. Trop.* 1960, Aug. 31, v. 40, No. 4, 579–600, 2 graphs. [34 refs.]

The author reviews all the examples of acute meningitis observed in the paediatric department of the Congolese Hospital at Luluaburg during the period July 1956 to December 1958, when 111 cases were recognized, representing 1·6–2·0% of all admissions. 18% of examples of acute meningitis occurred during the first month of life: among these the majority weighed less than 3 kgm. on admission. Only 5 affected children were more than 2 years old (4·5% of all cases).

The pneumococcus was found to be the most frequent agent being isolated from 55 patients, while other organisms affecting the meninges in early infancy included coliforms, salmonellae, *Proteus mirabilis* and a flavobacterium which is usually saprophytic. *H. influenzae* occurred in 34 instances, its greatest weight falling on infants under 6 months. Other rare organisms were a haemolytic streptococcus and *Neisseria catarrhalis*. In 12 instances Gram-stained smears and culture were negative.

Symptoms had usually existed for only one day before admission, fever, convulsions, crying, and refusal to suck being the most usual forms of presentation. Signs of acute meningitis were found to be far more difficult to recognize during the first month of life than after the third. Ocular signs however usually pointed to an intracranial lesion. Increased tension of the fontanelle is the second valuable sign. Among the less specific signs, grimacing is often seen in the youngest patients, while dyspnoea and tachypnoea without pulmonary cause may also indicate intracranial disease in the first few months of life. "Cardiac collapse" [probably vaso-motor collapse] was seen in 2 patients. Fever was seen in 57% of young infant patients, a subfebrile state in 27% while 16% were nonfebrile. After 6 months of age fever at onset was invariable.

The overall case mortality was 30%, though in the first month it was 47% and was even higher in premature infants weighing 2–2·5 kgm., of whom 8 out of 13 died. In older children the case mortality declined irregularly with increasing age, being about 20–30%. The case-mortality in pneumococcal meningitis was about 32%, with little variation among the age-groups up to 1 year. *H. influenzae* infections caused a case-mortality of 18·1%, with the heaviest toll in the first month of life.

The sex distribution of the fatalities was surprising, since among the female infants it was 12 out of 61 (19·6%) whereas in the males it was much higher at 20 out of 50 (40%). Sicklaemics appear particularly susceptible to the development of acute purulent meningitis.

Treatment was based on the use of tetracycline or oxytetracycline together with penicillin in pneumococcal infections and streptomycin for *Haemophilus* infections. An intrathecal injection daily for 8 days was also administered, penicillin in the case of pneumococcal and streptomycin in *Haemophilus* meningitis. *Salmonella typhi-murium* infection was treated with chloramphenicol and *Neisseria catarrhalis* by a combination of streptomycin and tetracycline. The aim was to maintain treatment until the cerebrospinal fluid had returned to normal the limits of hospital stay being 3 to 10 weeks.

J. H. Walters

EIGLER, J. O. C., WELLMAN, W. E., ROOKE, E. D., KEITH, H. M. & SVIEN, H. J. **Bacterial Meningitis. I. General Review (294 Cases).** *Proc. Staff Meetings Mayo Clinic.* 1961, July 19, v. 36, No. 15, 357–65.

This is the first of a series of articles which will appear in the Proceedings of the Staff Meetings of the Mayo Clinic on the subject of bacterial infections of the central nervous system. The records of 294 patients treated between 1948 and 1958 are reviewed and the cases are classified according to the causal organism. *Haemophilus influenzae, Streptococcus pneumoniae* and *Neisseria meningitidis* were cultured in 121 cases and these are not further discussed as the findings did not differ from those often reported. In 57 cases no organism was isolated, 33 of the patients having been treated by antibiotics before admission to hospital. In 116 cases bacteria "rarely associated with this disease" were isolated—*Streptococcus faecalis,* staphylococci, *Escherichia coli, Pseudomonas* and *Proteus* among others. In 141 instances there was underlying disease or injury.

A. B. Christie

BACTERIAL INFECTIONS

The order in this section is:—***General, Corynebacterium, Haemophilus, Enteric bacteria, Brucella, Pasteurella, Bacillus, Anaerobes, Spirochaetes, Others.***

NUCCIOTTI, L. Andamento della difterite in provincia di Cremona nel decennio 1951–1960. Considerazioni sulla vaccinazione antidifterica. [**The Trend of Diphtheria in Cremona Province in the Ten Years 1951–60**] *Igiene e San. Pubblica.* Rome. 1961, Mar.–Apr., v. 17, Nos. 3/4, 177–85. [10 refs.]

In a table the author shows data of diphtheria incidence, with rates per 10,000 inhabitants, in 6 countries including Italy itself and England [presumably with Wales] for each of the 10 years 1951–1960. The populations of Italy and of "England" are, according to the

author, more or less similar in size and their cases of diphtheria were respectively 12,961 and 849 in 1951, coming down to 9,612 and 357 in 1959. The drop in the incidence of diphtheria in Italy has been slower than in other comparable fully-developed countries. It is being urged that Italian children should be given diphtheria prophylactic, as recommended by WHO, between the 6th and the 12th months, with booster doses a year later and again at school entry.

Present Italian law requires immunization against diphtheria to be carried out between 1 and 2 years of age and the authorities recommend booster doses 3 and 6 years later, at ages 5 and 8. This practice has been strictly followed in Cremona with good results with alum-precipitated toxoid. The province had 47 cases of diphtheria in 1951 and only 1 in 1959; the search for carriers produced 10 in 1951 and 3 in 1959. The aim is to protect children in their most susceptible years, at ages 2–10.

It is true that Lombardy, a region which includes Cremona, has always had less diphtheria than many other parts of Italy, but the author believes that the results of immunization against diphtheria in the rest of Italy would improve if the law in the matter were thoroughly enforced, followed by booster doses at 2 successive intervals of 3 years. He does not think it is necessary to change and follow the procedure recommended by WHO. *J. Cauchi*

Berri, C. & Peretti, M. Osservazioni sullo stato immunitario antidifterico attuale dei soggetti vaccinati a Genova, in rapporto alla rivaccinazione. **[The Present State of Anti-Diphtheria Immunity in Immunized Persons in relation to Re-Immunization]** *Giorn. di Igiene e Med. Preventiva.* Genoa. 1960, July–Dec., v. 1, Nos. 3/4, 116–22. [10 refs.] English summary (8 lines).

In support of the desirability of efficacious artificial immunization against diphtheria from 6 months of age onwards, the authors point out that the serum antitoxin titre tends to fall rapidly and within a few years is often less than 0·01 IU/cc. with the consequent loss of resistance to infection. Re-immunization is thus necessary which they say should occur at 2–3 years of age, followed by repeater booster injections.

Using the tanned formolized sheep red cell agglutination test they tested sera from a group of children aged 6–10 in a children's home at Genoa. all of whom had been fully immunized and who 6–12 months previously had also been re-immunized with precipitated toxoid. The results were as follows: of 92 sera tested 37 showed less than 0·16 IU/cc., and 21 showed 0·5 IU or more. 28 showed practically no antitoxin level at all and this point is stressed in view of the booster injection only a relatively short time before. These 28 children and also 43 others with an antitoxin level of under 0·5 IU/cc. were re-immunized with the same antigen and their sera were tested 15 days later. 2 still showed no response, 64 had over 0·25 IU/cc. The authors express some doubts as to the duration of this immunity and state that it may even be necessary to consider annual booster injections. *W. K. Dunscombe*

Mishra, M. P. & Dave, D. S. **Enteric Fevers.** *J. Ass. Physicians India.* 1961, Mar., v. 9, No. 3, 243–52. [23 refs.]

Following upon the more effective control of malaria, the enteric fevers have become the commonest cause of prolonged fevers in India. Clinical experience with 232 cases admitted to hospital in Nagpur and Jabalpur is described; 210 were of typhoid fever, 18 of paratyphoid A and 4 of paratyphoid B, and the age range was 3 to 58 years.

Chloramphenicol was well tolerated and gave good results without serious complications. Dosage was usually 50 mgm. per kgm. daily and this was applied in 3 schemes; in schemes I and II the drug was given for 3 and 7 days respectively after the temperature touched normal, and in scheme III it was given for 7 days along with TAB vaccine 0·1, 0·2 and 0·3 cc. at 2-day intervals, followed by 2 further doses (0·5 and 0·5 cc.) after the drug was stopped. The relapse rate under schemes I and II was 35·2 and 14·8% respectively, while under scheme III it was only 2·2%. It is considered that such a combination of chloramphenicol and TAB vaccine gives the most satisfactory results, especially when the drug is started early in the disease. [An excellent article.]
H. Stanley Banks

Libov, A. **Enteric Fever in Children.** *Indian J. Pediatrics.* 1960, Apr., v. 27, No. 147, 125–8, 1 fig.

This is a short review of the main clinical findings in a series of 151 cases of typhoid fever in children aged 1–12 years admitted to a hospital in New Delhi. Among the 17 deaths in the series 5 were in patients moribund on admission. The diagnosis was confirmed bacteriologically or serologically in 70·8%. During treatment (with chloramphenicol) there was a marked decrease in the leucocytes in 5·3%, and agranulocytosis in 1 case. Relapses occurred in 11·9%.

The response to chloramphenicol, as judged by fall in temperature, was slow in comparison with that usually seen in adults; out of 92 patients treated the temperature fell within 6 days only in 8. Mortality among "vegetarians" was 3 times higher than that among "non-vegetarians", and it was thought that insufficient dietary protein lowered resistance. The author is dissatisfied with the results of chloramphenicol therapy alone, and thinks it should be combined with another antibiotic and with steroids. [The adverse local conditions may however have been responsible for the relatively poor results.]
H. Stanley Banks

Havlík, J. & Potuzník, V. Serologische Untersuchungen im Verlauf einer Bauchtyphusepidemie. **[Serological Investigations during an Epidemic of Typhoid Fever]** *Ztschr. f. Immunitätsf. u. Exper. Therap.* 1961, June, v. 121, No. 4, 311–24. [11 refs.]

A small epidemic of typhoid fever occurring in Czechoslovakia has been studied especially in respect of the influence of chloramphenicol treatment on the

evolution of antibody formation in the patients. The immune response was studied by the older method of direct agglutination, with O, H and Vi antigens, and also by the Coombs modification in which the bacteria first exposed to the patient's serum are then washed and exposed to an anti-human-globulin serum, and lastly by the agglutination of antigen-coated red corpuscles. The supernatant from a suspension of washed typhoid bacteria, steamed for 2 hours and then centrifuged, was used as antigen in coating the red blood corpuscles. The general result of these investigations was to show that in a group of sporadic cases, mostly mild, the response in agglutinin production was poor.

In a second group of cases which developed with epidemic abruptness the disease was more severe and the response usually took the forms of a rising and falling curve of agglutinins. Observations were made at weekly intervals. The direct observations on agglutination were the most disappointing and the indirect method of agglutination of sensitized red blood corpuscles was the most satisfactory. A surprising feature was the frequent absence of H agglutinin and in some cases also of Vi agglutinins. The O agglutinins gave the most satisfactory results, the reaction developing earlier and being more pronounced than with the other antigens. The O strain used had the antigen formula 9,12. For H agglutination the strain Virginia 8 (d) was used and for Vi agglutination Vi 1 (Bhatnagar). *J. W. McLeod*

EASTWOOD, J. **Oral Humatin (Paromomycin) in Chronic Enteric Carriers.** *J. Hygiene.* 1961, Mar., v. 59, No. 1, 65–76. [17 refs.]

A clinical trial of oral Humatin therapy was carried out in 27 chronic carriers of typhoid and paratyphoid B bacilli in a mental hospital. This drug is an antibiotic which is very poorly absorbed from the gut, and which therefore maintains a high faecal concentration and low blood and urinary concentrations. In this trial it apparently rendered the faeces free from the specific organisms during the period of administration of the drug only; it is suggested that the action of the drug may be bacteriostatic rather than bactericidal, although the factor of access to the persistent foci of infection may also be concerned. It is concluded that the drug fails, in the dosage given (4 to 6 gm. daily for 6 days), to cure the carrier state. [In this connexion attention may be directed to the high success obtained with surgical methods in a recent article—9 cases, 9 successes (MAIN, this *Bulletin*, 1961, v. 36, 666).]

H. Stanley Banks

ENGELHARDT, H. Experimentelle Beiträge zur oralen Typhusimmunisierung. **[Experimental Contributions to Oral Immunization against Typhoid Fever]** *Ztschr. f. Immunitätsf. u. Exper. Therap.* 1961, v. 121, No. 5, 437–43, 4 figs.

The English summary appended to the paper is as follows:—

"No basic immunization could be demonstrated by per os application of vaccine in mice and monkeys.

"Immunity produced in mice by subcutaneous immunization could not be influenced by a fourth oral application of vaccine in the way of a booster-reaction."

RICHARDS, C. S., JACKSON, W. B., DECAPITO, T. M. & MAIER, P. P. **Studies on Rates of Recovery of *Shigella* from Domestic Flies and from Humans in Southwestern United States.** *Amer. J. Trop. Med. & Hyg.* 1961, Jan., v. 10, No. 1, 44–8.

The studies described in this paper were done on flies, captured out of doors with a cone net and indoors with a portable vacuum cleaner, from two American Indian villages in an arid region of south-central Arizona where measurements of the incidence of diarrhoeal disease and the prevalence of shigellosis were in progress. Flies were transferred from their respective traps to suitable containers after identification and kept in pools under CO_2 snow until they could be examined. They were then thawed, crushed and ground up in a fluid culture medium. The deposit, after centrifugalization, was inoculated onto plates of a differential agar medium and incubated for 24 hours when colony selection, followed by biochemical and serological examination, enabled the identification of shigella organisms, if present to be confirmed.

Outdoor collections totalled 65,273 flies and from these there were 69 shigella isolations; indoor collections totalled 5,664 flies from which there were 12 shigella isolations. There were 11 shigella serotypes isolated from the flies and the same 11 types were isolated, in a sampling survey from the local population. There was a good deal of evidence to correlate the isolation rate from flies and the isolation rate from rectal swabs of the people, but the indices were too low to provide a sufficiently sensitive and effective means of measuring the prevalence of *Shigella* infections in these particular areas. *Musca domestica* was the most abundant species of fly collected and most of the flies from which shigella organisms were isolated belonged to this species.

H. J. Bensted

KUBINYI, L. A nagybátonyi és sztálinvárosi enterális járványok okai. **[The Causes of the Epidemics of Dysentery in Nagybátony and Sztálinváros]** *Népegészségügy.* Budapest. 1961, June, v. 42, No. 6, 176–81, 192, 5 figs. German summary.

An account is given of 2 outbreaks of dysentery occurring in Hungary which were due to faulty planning and construction of sewerage and water supplies. In 1959 an epidemic of dysentery with a total of 1065 cases occurred among 8,000 inhabitants of the mining town of Nagybátony; *Shigella flexneri* 3 was isolated from the stools of 602 patients. The water main had 2 branches, which supplied residential areas on a hill and in a valley. Owing to a shortage of water periodical interruption in the supply took place, leading to negative pressure in the mains; as a result of this sewage from a blocked sewer was aspirated through a break in the mains and gained access to the water supply.

In 1960 an outbreak of dysentery occurred in the town of Sztálinváros, with 220 cases and an incidence of

about 10%. The infection was due to the fact that the water was not chlorinated, and a well from which it was derived had been sunk too near to the bed of the Danube. *D. J. Bauer*

PAJOR, Géza. A répceszentgyörgyi dizentéria járvány. [**The Outbreak of Dysentery in Répceszentgyörgyi**] *Népegészségügy*. Budapest. 1961, June, v. 42, No. 6, 181–4, 192, 1 diagram. German summary.

The author describes an outbreak of dysentery which occurred in a children's institute in Hungary in 1959. The infection was derived from a well supplying drinking water which was contaminated with sewage. 119 (56·4%) children and staff members developed the disease among a total of 211 at risk. *Shigella flexneri* was isolated in 35 instances, *Sh. schmitzii* (*dysenteriae* 2) in 26, *Escherichia coli* O 124 in 7, *Sh. flexneri* and *Sh. schmitzii* together in 4 and *Sh. flexneri* and *E. coli* O 124 together in 1 instance. *D. J. Bauer*

SOLOMON, P., WEINSTEIN, L. & JORESS, S. M. **Studies of the Incidence of Carriers of Enteropathogenic *Escherichia coli* in a Pediatric Population.** *J. Pediatrics*. St. Louis. 1961, May, v. 58, No. 5, 716–21. [15 refs.]

This study involved just over 1,000 children mainly in the lower age-group, 0–2 years, and the *Escherichia coli* carriers identified belonged to the enteropathogenic O-types: O26; O55; O86; O111; O119; O124; O125; O126; O127; O128. The incidence of the asymptomatic carriage rate was 5·6%. Of those children under the age of 2 years from whom enteropathogenic *E. coli* were isolated 41% showed no evidence of any intestinal disorder, and 47% of the patients from whom one of the recognized enteropathogenic types was isolated also harboured a further serotype of the same group. As the age-group advanced so did the proportion of the symptomless excreters. Thus in the absence of any epidemic of enteritis this high incidence of the asymptomatic carrier state made it extremely difficult to judge the significance of the enteropathogenic serotype isolated. *H. J. Bensted*

STENZEL, W. *Proteus inconstans* O 13 H 30 als Enteritiserreger bei Kleinkindern. [***Proteus inconstans* as Cause of Enteritis in Infants**] *Zent. f. Bakt.* I. Abt. Orig. 1961, v. 182, No. 2, 178–83. [20 refs.]

The micro-organism discussed has been described by different workers as a type of paracolon bacillus as Providence and as *Proteus inconstans* [this *Bulletin*, 1956, v. 31, 447], the last being the name accepted in the Bergey nomenclature.

Typically this bacterium fails to ferment lactose, mannite, arabinose and sorbite and does not decompose urea or H_2S. Glucose is fermented and indole is produced. Most strains are motile but those which are not may be distinguished from the *Shigella* by fermentation of adonite and inosite. A dark red colour on Kligler medium is characteristic.

The author observed a child with fever and diarrhoea whose stools yielded practically pure cultures of this bacterium on Endo and Leifson media before any antibiotic had been administered. The attack came to an end on administration of chloramphenicol and the serum showed a low titre of agglutinins for the bacterium concerned, but none for the typhoid-paratyphoid group. These observations led him to investigate the incidence of this micro-organism more extensively. One strain was obtained from sputum, 16 from urine, 7 from stools in cases of enteritis and 53 from the stools of healthy persons.

4 of the strains from the enteritis cases corresponded immunologically with the first patient's strain but only one of those from the healthy persons. There was no marked rise in the serum agglutinin of the patients infected. The author points out, however, that the value of this evidence is diminished by the fact that the normal persons examined were mostly adults and the patients mostly children—further investigation is required. *J. W. McLeod*

DE TORREGROSA, M. V. & ORTIZ, A. **Severe Infections in Children due to Rare Gram-Negative Bacilli (*Mima polymorpha* and *Bacillus anitratum*).** *J. Pediatrics*. St. Louis. 1961, July, v. 59, No. 1, 35–41, 2 figs. [17 refs.]

Short case histories are presented of 7 patients, all infants, with severe infections caused by organisms of the tribe Mimeae: 3 cases of meningitis and 2 of septicaemia due to *Mima polymorpha*, and 2 of septicaemia due to *Bacterium anitratum*. 3 of the patients died.

Mimeae, so-called from their ability to mimic other organisms, have been isolated from normal persons and rarely cause serious infections, but may be mistaken for other organisms, *Neisseria* especially, if infections are diagnosed by morphology alone. Mimeae can be distinguished from neisseriae by their ability to grow readily on unenriched media, *e.g.* MacConkey agar, on primary isolation (although some strains of *M. polymorpha* are oxidase positive), and from each other by carbohydrate fermentation, growth in citrate, and ability to reduce nitrates.

They show no characteristic antibiotic sensitivity pattern but most strains are sensitive to broad-spectrum antibiotics, particularly oxytetracycline. Only one penicillin-sensitive strain of *M. polymorpha* has been reported.

[See also this *Bulletin*, 1960, v. 35, 155.] *A. C. Scott*

REVICH, S. J., WALKER, A. W. & PIVNICK, H. **Human Infection by *Brucella abortus* Strain 19.** *Canadian J. Pub. Health*. 1961, July, v. 52, No. 7, 285–9. [22 refs.]

Accidental infections by *Brucella abortus* strain 19, giving rise to clinical illnesses among veterinary workers, are by no means rare, but these infections are generally

contracted during the administration of the live vaccine by splashes falling on to the conjunctivae or by mishaps with the loaded syringe resulting in actual injection of the vaccine.

In the case reported in this paper, the victim was a laboratory worker who accidentally sucked the culture into his mouth through faulty pipetting technique. The mouth was rinsed out with water but no other protective measures were taken. The dose taken was estimated at 5 x 10^9 bacterial cells and the clinical illness was manifest 8 days later. *Br. abortus* was not isolated from the blood but specific agglutinins in rising titre established the diagnosis. There was nothing exceptional about the illness and this laboratory infection has interest only because it is the first reported human accidental infection with *Br. abortus*, strain 19, *via* the oral route.

H. J. Bensted

KUROKAWA, T., MASUDA, H., ICHIKAWA, K., SATO, M. & OHARA, S. **Studies on the Skin Test of Yato-Byo (Ohara's Disease, Tularemia in Japan). Fourth Report: Results of the Skin Test in Miyagi Prefecture.** *Tohoku J. Exper. Med.* 1961, Feb. 25, v. 73, No. 3, 268–73, 1 fig.

This study was undertaken in the prefecture of Miyagi, which is in the N.E. part of the main island of Japan where *yato-byo*, or Japanese tularaemia, may be said to be endemic. The antigen used for the mass skin-testing of populations of towns and villages was a heat-killed, phenol-preserved, suspension of a virulent strain of *Brucella tularensis* injected intradermally. No information is given about the value of this skin test as a diagnostic tool in determining tularaemic infections, either latent or overt, but the test appears to be accepted by the Japanese workers concerned as specially suitable for surveys of this sort. This form of tularaemia is said to resemble closely tuberculosis in its general pathology and in its histological features and the possible relationship between the tuberculin reaction and the *yato-byo* was considered, but there was no evidence of any correlation between the two tests; the *yato-byo* skin test was accepted as highly specific and entirely suitable for epidemiological studies of this tularaemic infection.

H. J. Bensted

BRACHMAN, P. S., PAGANO, J. S. & ALBRINK, W. S. **Two Cases of Fatal Inhalation Anthrax, One associated with Sarcoidosis.** *New England J. of Med.* 1961, Aug. 3, v. 265, No. 5, 203–8, 4 figs.

This paper contains a very detailed account of 2 fatal cases of inhalation anthrax with full descriptions of the clinical, X-ray and other pathological findings. The first case occurred in 1957 in a Negro aged 28 who also had a 2½-year history of confirmed sarcoidosis. Epidemiological investigation of this case led to the further consideration of a second case of fatal inhalation anthrax in a housewife aged 50, which had occurred in the vicinity about 8 years previously. In neither case was there a history of occupational exposure to anthrax but in the neighbourhood was a tannery in which imported goat skins were processed. Examinations of surface swabs from the receiving area of the tannery and floor sweepings were positive for anthrax bacteria. There was no record of any case of inhalation anthrax at the tannery but a case of cutaneous anthrax had occurred in 1945. The Negro patient walked daily past the open area where the hides were received into the tannery and the housewife had lived 1½ blocks on the other side of the tannery. Nevertheless, the reasons for these 2 persons contracting anthrax remain obscure.

In the discussion the possible influence of pre-existing systemic sarcoidosis on the development and clinical course of inhalation anthrax is examined.

M. E. Delafield

WILKINSON, J. L. **Neonatal Tetanus in Sierra Leone.** *Brit. Med. J.* 1961, June 17, 1721–4. [19 refs.]

This report from the Nixon Memorial Hospital, situated at Segbwema in the South-Eastern Province of Sierra Leone, describes the treatment of 114 consecutive cases of neonatal tetanus. Chlorpromazine became available during the course of the study and was added to treatment, and the latter half of the series serves to evaluate its action.

The area is largely underdeveloped and all the patients came from primitive villages where they had been delivered by traditional village midwives. After delivery the umbilical cord is cut with a special knife kept in the hut of an elder in each village, the stump is ligatured with locally-spun thread and the gummy juice of a young banana shoot, squeezed out by hand, is then applied and is reapplied daily. This substance may well be the source of infection, for the young shoots arise below ground at the base of the tree around which the domestic rubbish is thrown, thus attracting domestic animals, goats, sheep, hens and pigs, which root in it for food.

The series contained 60 boys and 54 girls, the predominant numbers occurring in the wet season. Most cases were severe, the average duration of life of those who died after admission being only 2·4 days. As usual, the shortness of the incubation period reflected the severity of the attack, those infants who survived having a mean age of 10·5 days on admission as compared with 6·3 days for those who died. Inability to suck due to trismus was the usual presenting sign, after which generalized muscular spasms quickly ensued.

Nursing care comprised feeding with expressed breast milk *via* a fine naso-gastric tube, cleansing of the umbilicus with hydrogen peroxide followed by the application of a dry dressing, and aspiration of pharyngeal secretions. Specific therapy was initiated with an injection of antitetanic serum, the dosage of which varied from 20,000 to 50,000 units, according to severity, prior to the introduction of chlorpromazine but was standardized at 10,000 units thereafter: only a single dose was given. Penicillin in oil was given to every patient, in an initial dose of 300,000 units, followed by 150,000 units daily for 5 days. The sedatives used during the first half of the period under review comprised chloral and potassium bromide, supplemented when necessary with intramuscular injections of phenobarbitone sodium and, in 1 patient, paraldehyde. The later patients were sedated with chlorpromazine by intramuscular injection, 10 mgm. being given

every 4 hours for the first 24 hours, thereafter every 6–8 hours. This was required by those who survived for an average of 9·6 days, the longest period of sedation being 17 days. Mephenesin (Myanesin) was given as 3·5 ml. of the elixir every 6 hours by gastric tube to 24 infants before chlorpromazine was available.

In the pre-chlorpromazine series, 27·3% lived, 54·5% died and 18·2% probably died after removal from hospital (total mortality 72·7%). Of 24 infants [presumably included in the above series] who received mephenesin 79·2% died. The case mortality of the infants sedated with chlorpromazine contrasted sharply with the former results, for 51·4% survived while only 31·4% died in hospital, though the fate of 12 who were removed prematurely is unknown, and they were presumed to have died. This favourable result is statistically significant.

The author discusses the optimal dosage of chlorpromazine and notes that other workers have recorded less favourable results when using higher dosages [see, for example, this *Bulletin*, 1960, v. 35, 580]. He concludes that his initial dosage of 4·5 mgm. per kgm. daily in divided doses was probably too high, and in later cases employed 2·3 mgm. per kgm. [stated erroneously to be equivalent to 5 mgm. per lb.; the figure should be 1·05 mgm. per lb.]. Additional sedation may be achieved by the use of small doses of barbiturates. Mephenesin appears to be without benefit in the dosage used.

J. H. Walters

Botticelli, J. T. & Waisbren, B. A. **Tetanus in an Urban Community.** *Amer. J. Med. Sci.* 1961, July, v. 242, No. 1, 44–50. [10 refs.]

The authors review 9 cases of tetanus seen in an urban community in Wisconsin during an 8-year period. 2 of the patients had been treated with penicillin soon after injury, in one case 12 hours after, and in another 2 days after but both patients developed fatal attacks of tetanus. The authors stress the fact that penicillin does not prevent the onset of tetanus. Treatment followed the usual lines and the authors state that active or passive immunization against tetanus would probably have prevented all the attacks.

A. B. Christie

Rojas, M., Weitman, J., Moya, H., Segovia, M., Jimenez, L., Villalobos, Maria, Tello, A. & Rodo, F. Experiencia en 63 casos de tétanos. [**Tetanus. Report of 63 Cases with special reference to Modern Management**] *Rev. Med. Chile.* 1960, May, v. 88, No. 5, 349–58. [25 refs.] English summary.

This is a review of the treatment of 63 patients suffering from tetanus, treated in hospital in Santiago, Chile, between 1950 and 1958. 23 patients died, a mortality of 36·5%, but of 17 severely ill patients 12 died, a mortality of 71%. There was a direct relationship between mortality and length of incubation period, period of onset, frequency of spasms and severity of spasms. Treatment followed the usual lines of sedation, antitoxin, antibiotics and tracheotomy. Expert team work is essential and had it been available for all cases, mortality might have been reduced.

A. B. Christie

Patel, L. R. & Parikh, N. K. **Further Observations on Treatment of Tetanus.** *J. of J.J. Group Hosps. & Grant Med. College.* Bombay. 1961, July, v. 6, No. 3, 207–14. [12 refs.]

The authors, in Bombay, treated 84 patients suffering from tetanus with combinations of gallamine and chlorpromazine: 26 "control" patients were treated with mephenesin and phenobarbitone. They found that spasms were better controlled by gallamine and chlorpromazine. Patients were classified according to severity on the basis of length of incubation and onset periods. In the most severe group, with an incubation period of less than 7 days and an onset period of less than 24 hours, mortality rate was not improved—the only "control" patient in this group died, and 17 of 19 in the treated group. In less severe cases, the authors claim that mortality was reduced. [Some of the figures quoted are difficult to follow. Gallamine is also known by the proprietary name Flaxedil.]

A. B. Christie

Forbes, J. A. **The Management of Tetanus.** [Correspondence.] *Med. J. Australia.* 1961, July 8, v. 2, No. 2, 72–3.

The author refers concisely to the treatment of 34 patients suffering from tetanus and analyses clearly the severity of the different clinical types. Confusion regarding claims for different treatments arises from different assessments of what constitutes severe tetanus. Persistent severe spasms may cause respiratory impairment and in these cases curare, tracheotomy and artificial ventilation may be the only hope of cure. Spasm of the larynx and pharynx may also cause respiratory obstruction and tracheotomy with a less powerful relaxant may suffice. In less severe cases, with no respiratory obstruction, sedation is usually sufficient. When artificial respiration is required the author prefers tank respiration to intermittent positive pressure. For an adult 100,000–150,000 units of antitoxin provides an excess of circulating antitoxin for several weeks and repeated doses are unnecessary. [This is a preliminary report only.]

A. B. Christie

Smith, C. E. G., Turner, L. H., Harrison, J. L. & Broom, J. C. **Animal Leptospirosis in Malaya. 1. Methods, Zoogeographical Background, and Broad Analysis of Results.** *Bull. World Health Organization.* Geneva. 1961, v. 24, No. 1, 5–21, 3 figs. [22 refs.] **2. Localities Sampled.** *Ibid.*, 23–34, 1 fig.

1. 30 of each of the principal animal species in selected areas of forest, ricefields, scrub and grassland, and towns and villages were trapped, and examined by serological and culture methods for evidence of leptospirosis.

120 strains of leptospires were isolated, 92% of them from rats, and serological evidence of infection, by almost every leptospiral serogroup, was found in a wide range of animal species, including reptiles.

The incidence of leptospirosis in the different species trapped in each area, the distribution of leptospiral serogroups in different hosts, and the animal species infected with each serogroup, are recorded; the survey

methods used are compared, and the factors influencing the degree of risk to man and domestic animals, and the risk of infection in the four types of locality studied, are discussed.

The "carrier efficiency" of each species can be estimated by comparing the numbers of infected animals diagnosed by serological and culture methods; if these are equal infection is persistent and the species an efficient carrier. 4 of the 12 rat species examined were found to be efficient carriers.

It is concluded that leptospirosis in Malaya is maintained wholly or mainly by rats; infection of man and domestic animals is incidental and contributes little to maintenance of the disease.

2. Each of the four types of area studied had a characteristic rat population, including one species with a higher infection rate and of more importance as a maintenance host.

In towns and villages the main rat hosts are *Rattus rattus diardi* and *R. norvegicus*; in ricefields *R. exulans* and *R. argentiventer*; in secondary forest and scrub (where the fauna overlaps with that of primary forest) *R. exulans* and *R. jalorensis*, and in primary forest giant, and to a lesser extent spiny rats.

From a consideration of rat population densities and species infection rates it is calculated that two or more rats of the maintenance species per hectare are necessary to maintain leptospirosis in the rat population.

The living habits of different rat species can be inferred from their rate of infestation by trombiculid larvae; by correlating this with the rate of infection by leptospirae it is concluded that ground-living species are more efficient maintenance hosts than those which scramble on vegetation or are tree-living. *A. C. Scott*

Smith, C. E. G. & Turner, L. H., with the technical assistance of J. B. H. Adam. **The Effect of pH on the Survival of Leptospires in Water.** *Bull. World Health Organization.* Geneva. 1961, v. 24, No. 1, 35–43, 1 fig. [21 refs.]

When cultures of 4 leptospiral serotypes were added to distilled water buffered to *p*H levels of 5·3 to 8·0, all survived longer in alkaline than in acid solutions and variations in *p*H produced significant differences in the survival times of the different serotypes.

No significant differences were noted when different serotypes were added to aqueous extracts of soils; all the extracts tested were acid, however, and it is suggested that differences would have occurred if alkaline extracts of soil had been examined.

In the South Kedah group of ricefields in Malaya, based on montmorillonite clay, despite a high incidence of rat leptospirosis there is a low incidence of human leptospirosis which cannot be explained by the *p*H or salinity of the water. Pilot experiments, in which bentonite (a mineral similar to montmorillonite) added to leptospiral suspensions halved the number of leptospires remaining in suspension, suggested that adsorption of leptospires by soil particles may be important in reducing the number of free leptospires in the water of this group of ricefields, and under similar conditions elsewhere. *A. C. Scott*

Parnas, J., Lazuga, K., Dabrowski, T. & Kóslak, A. **Strains of Leptospirae evoking Swamp Fever in Southeastern Poland: a Four-Year Survey.** *J. Infect. Dis.* 1961, May–June, v. 108, No. 3, 243–6. [16 refs.]

The authors present tabulated details of their findings, serological and cultural, in wild animals, domestic livestock and human beings: these were obtained in southeastern Poland during 1955–1959 [see also this *Bulletin*, 1960, v. 35, 1119].

The main reservoir hosts were *Mus musculus, Microtus arvalis, Arvicola terrestris, Microtus ratticeps, Erinaceus roumanicus* and *Sorex araneus*. The carrier rate tended to vary from year to year, as did the ratio of carrier rate to seropositivity rate. The commonest serotypes isolated were *Leptospira grippotyphosa* and *L. sejroe*; the following serotypes were occasionally isolated—*L. saxkoebing, L. sorex, L. australis A, L. icterohaemorrhagiae* and *L. bataviae*.

Agglutination tests of serum showed that serotypes other than these also reacted on occasion but the predominant reactors were *L. grippotyphosa* and *L. sejroe*. [It is also apparent from the tables that a few seronegative animals, of various species, yielded positive kidney cultures.]

The distribution of agglutination reactions, with various serotypes, in the human patients broadly followed that of the rodents.

The authors note that, in 1959, birds were examined but that none was found to be serologically positive and no isolates were obtained. [The number and species of the birds examined are not given.] *L. H. Turner*

Vosta, J. Leptospirosní ohniska na Táborsku. [**A Focus of Leptospirosis in Tábor**] *Českoslov. Parasit.* Prague. 1961, v. 8, 403–14, 6 figs. [20 refs.] German summary (8 lines).

In a field investigation of a natural focus of leptospirosis in the area of Tábor in Southern Bohemia 679 rodents and insectivores belonging to 14 species were examined in the agglutination-lysis test with 12 species of *Leptospira*. Serological evidence of infection with *L. grippotyphosa* was found in 1 of 2 moles (*Talpa europea*), 3 of 51 shrews (*Sorex araneus*), 1 of 27 bank voles (*Clethrionomys glareolus*), 36 of 216 (16·7%), common voles (*Microtus arvalis*), 6 of 77 musk rats (*Ondatra zibethica*) and 6 of 69 long-tailed field mice (*Apodemus sylvaticus*); infection with *L. sejroe* was found in 13 of 105 (12·4%) house mice (*Mus musculus*). Histological evidence of infection was found in 55 animals (mainly *Microtus arvalis* and *Mus musculus*). 6 strains of *L. grippotyphosa* were isolated from *Microtus arvalis* and 4 strains of *L. sejroe* from *Mus musculus*. In the investigation of sera from 434 larger animals infection with *L. grippotyphosa* was found in 28 of 400 (7%) hares, and among 501 domestic animals 7 of 76 dogs (9·2%), 23 of 100 pigs, 77 of 168 cattle (45·8%) and 7 of 37 goats (21·6%) were found to have antibody. *D. J. Bauer*

Füzi, M. & Kiszel, J. Leptospirózis vizsgálatok a Tápió vidéken. [**Investigations on Leptospirosis in the Province of Tápió**] *Népegészségügy.* Budapest. 1961, June, v. 42, No. 6, 184–8, 192. [13 refs.] German summary.

In 1954 an epidemic of leptospirosis occured in the Tápió province of Hungary, with a total of 22 cases. The course was mostly mild, without jaundice, and there were no fatal cases. The diagnosis was confirmed by the agglutination-lysis test in 10 patients; development of antibody to *Leptospira pomona* was observed in 4, to *L. grippotyphosa* in 4 and to *L. hyos* in 2 patients. The last 2 species had not previously been observed in this area. Infection was probably derived from bathing in a river or from contact with animals. In a serological investigation of 50 pigs in the area antibody to *L. hyos* was found in 17, to *L. pomona* in 12, and *L. sejroe* in 2 animals, and combinations of these in 11; of 40 cattle 8 had antibody to *L. pomona*, 2 to *L. sejroe* and 1 to *L. grippotyphosa*, and 2 to both *pomona* and *sejroe*, and 4 of 42 sheep had antibody to *L. icterohaemorrhagiae*.

D. J. Bauer

Rafyi, A. & Maghami, G. Sur la fréquence de leptospirose en Iran. III. Isolement de *Leptospira grippotyphosa* (=*L. bovis*) chez les ovins. [**Incidence of Leptospirosis in Iran. III. Isolation of *Leptospira grippotyphosa (L. bovis)* from Sheep**] *Bull. Soc. Path. Exot.* 1961, Mar.–Apr., v. 54, No. 2, 179–81.

Roth, E. E., Adams, W. V. & Linder, Donna. **Isolation of *Leptospira canicola* from Skunks in Louisiana.** *Pub. Health Rep.* Wash. 1961, Apr., v. 76, No. 4, 335–40. [25 refs.]

Most of the skunks were collected in south central Louisiana between the Mississippi and Atchafalaya Rivers. The area is primarily agricultural with a moderate population of cattle and dogs but heavily populated with striped skunks (*Mephitis mephitis*).

Since February 1959, 180 strains of leptospires have been isolated from 310 striped skunks: 7 have already been identified as *Leptospira pomona*, and 5 others (the subject of this paper) were found to be identical with *L. canicola* (strain Hond Utrecht IV). All 5 strains were isolated by the agar plate method described by Cox and Larson [this *Bulletin*, 1957, v. 32, 999] and 4 of the strains were obtained in pure culture by direct inoculation of semi-solid media: 10% kidney suspension was used as inoculum. Initial screening, and cross-agglutination, studies showed that the 5 strains behaved similarly to *L. canicola*: cross agglutinin-absorption tests confirmed their identity.

The 5 skunk sera were tested (agglutination) with 21 serotypes: the titres with *L. canicola* were 1 in 300 (4 sera) and 1 in 1,000; heterologous titres of 1 in 30 or 1 in 100 were found for *L. ballum* and *L. pyrogenes*; and one serum also agglutinated *L. hardjo*, *L. seiroe*, and *L. medanensis* to 1 in 100.

Skunks have now been proved to carry several serotypes of *Leptospira* in the United States including *ballum* [this *Bulletin*, 1959, v. 34, 538] and members of the *hyos* and *hebdomadis* groups [*ibid.*, 1961, v. 36, 402]. These infections appear not to be fatal; and gross kidney lesions are minimal and undetectable in most of the animals found to be carriers.

The epizootiological picture is thus further complicated in respect of *L. canicola* infection in the United States. As skunks feed among resting cattle at night, the possibility of interspecies transmission to livestock is very likely. Moreover, pet skunks may be a hazard to human beings and domestic animals.

[This paper includes a useful summary, and bibliography, of *L. canicola* infections in animals reported from various parts of the world.] *L. H. Turner*

Dungal, N. **Listeriosis in Four Siblings.** *Lancet.* 1961, Sept. 2, 513–16, 5 figs. [14 refs.]

Listeria monocytogenes may cause disease in the newborn presenting as (a) a septic generalized infection, (b) meningitis, and (c) encephalitis or meningoencephalitis. This article reports the probable occurrenc of listeriosis in 4 children of one mother: the first 3 died in infancy and post-mortem examination of the third failed to reveal the cause of death though some dissolution of brain tissue and gliosis was seen. Caesarean section was carried out at the 4th month of the 4th pregnancy and the foetus examined: *L. monocytogenes* was isolated from the amniotic fluid. The mother was treated with oxytetracycline during a 5th pregnancy and a normal child was born. [There is a full discussion which must be read in the original.] *A. B. Christie*

McKinnon, D. & Swithinbank, J. M. **Meningitis due to *Listeria monocytogenes*.** *Lancet.* 1961, Sept. 2, 516–17. [14 refs.]

The authors record the occurrence of meningitis in a man aged 53. From the cerebrospinal fluid an organism resembling a diphtheroid was cultured, later proved to be *Listeria monocytogenes*: it was insensitive to tetracycline and sulphonamide but sensitive to penicillin, streptomycin, chloramphenicol, erythromycin, novobiocin and furaltadone. The patient was treated with streptomycin, penicillin and chloramphenicol but died on the 4th day after admission to hospital. A domestic cat which had a suppurating wounded ear may have spread the infection, but the infecting organism of the cat was not investigated. *A. B. Christie*

Moppert, J. Listeriose. Eine weitere Beobachtung von Granulomatosis infantiseptica in der Schweiz. [**A Further Observation of "Granulomatosis Infantiseptica" in Switzerland**] *Schweiz. med. Woch.* 1961, July 1, v. 91, No. 26, 784–6, 4 figs. [26 refs.]

A further case of general infection *in utero* with *Listeria* is described since it is still a rarity in Switzerland.

The mother became fevered in the eighth month of pregnancy and gave birth to a still-born infant. The post mortem of the foetus revealed a wide distribution of necrotic foci, pinhead in size and often associated with haemorrhage. These were especially notable in the liver and in the membranes at the base of the brain.

Pure cultures of *Listeria* were recovered from all viscera examined and the micro-organism was found to belong to the immunological type I. No antibodies could be recognized in the mother's serum. She had, however, the history of an abortion two years earlier.

J. W. McLeod

VIRUS INFECTIONS

The order in this section is:—***General, Psittacosis, Lymphogranuloma group, Pox group, Respiratory group, Reovirus group, Enteric group, Arthropod-borne group, Others.***

Soc. Ital. Per Lo Studio Delle Malattie Infettive e Parassit. Simposio i cortisonici nelle malattie virali, S. Margherita Ligure, 11–12 luglio 1960. **[Symposium on Cortical Hormones in Virus Diseases]** *Giorn. di Malattie Infettive e Parassit.* 1960, Dec., v. 12, No. 12, 947–1165, numerous figs. [Numerous refs.]

This symposium comprises 47 papers and accounts of the discussions they provoked, and is divided into 9 sections. The first section is on the metabolic effects of cortical hormones, the next 7 sections are devoted to discussions of the treatment of virus diseases with these substances—measles, erythema multiforme, mononucleosis, the pox diseases, mumps, hepatitis, influenza and other respiratory diseases, the diseases of the nervous system—and the final section in general. Some of the papers are quite lengthy, but others are little more than short notes; many are comprehensive summaries of relevant literature but others report original work.

It is not feasible to give here an account of this mass of information, but the general sense of the symposium was summed up at the end by De Toni (pp. 1164–65), who made the following points:—

The possible actions of cortical hormones on virus diseases include interference with cell metabolism, especially protein metabolism, and this is linked with the fact that virus infection itself actually stimulates protein metabolism. The hormones modify the interaction between virus and cell by reducing the respiratory activity of the mitochondria, with corresponding diminution of the energy available for the processes of protein synthesis. Multiplication of virus is not necessarily inhibited in this process, and for some viruses (polio, vaccinia, equine encephalomyelitis) multiplication remains unaltered.

The corticosteroids restrict the reactivity of the mesenchyme, and possess anti-histamine, anti-hyaluronidase, anti-exudative and anti-inflammatory properties; they also suppress or retard the production of antibodies. These effects may be favourable in certain virus diseases, especially in those in which the symptoms are especially related to the activity of the inflammatory response rather than to the direct action of the virus; there is, however, insufficient limitation of lesions and consequent spread of virus because the formation of antibodies is insufficient.

The hormones also act by reducing fever and improving the general condition, and this may be advantageous provided that the progress of the disease is not thereby masked.

Observations made on virus diseases in experimental animals, or in tissue cultures, may differ markedly from those in man, and are due to differences in dosage, susceptibility of experimental animals, and tempo of administration of the cortical hormones.

In man 3 groups of virus diseases may be distinguished clinically. In the first group treatment with hormones is clearly indicated—hepatitis (particularly), and infection of the nervous system secondary to virus infection or vaccination, in which high dosage can alter the prognosis rapidly. In the second group the hormones (in moderate dosage) are harmless and are indicated when their use reduces the symptoms or inflammatory response in grave cases in which these reactions are not fundamentally of the first importance in pathogenesis—for instance in infantile stenosing laryngitis, mumps and its complication orchitis, measles, vaccinia and herpes with excessive toxicity, and poliomyelitis with congestion and oedema accompanying the destruction of nerve tissue.

In the third group are diseases like chickenpox in which the use of corticosteroids may be dangerous and fatal, but here the question of timing and dosage is important, for in most fatal cases prior and intense cortical hormone therapy has been instituted for some other reason. But by continuation of this therapy it is possible to avoid the dangerous reactions which may occur on the sudden withdrawal of the treatment. Institution of hormone therapy *de novo* may reduce the possibility of nervous or pulmonary complications.

Charles Wilcocks

Corlett, Keitha. **Viral Infections of the Central Nervous System. A Survey from the Auckland Hospital, April, 1960 to March, 1961.** *New Zealand Med. J.* 1961, June, v. 60, No. 346, 241–53.

"One hundred and nine cases of apparent viral infection of the C.N.S. were studied in an attempt to establish an etiological agent by clinical examination, tissue culture, and serological techniques. The cases were divided into three groups—32 of encephalitis, 61 of lymphocytic meningitis, and six of paralytic poliomyelitis.

"Of the 32 cases of encephalitis a definite etiological agent was found in 12, six due to varicella, five to mumps and one to morbilli. A possible etiological agent was found in six cases: two due to herpes, one mumps, one rubella, one E.C.H.O.–14, and one infectious mononucleosis.

"Thus, a definite or possible etiological agent was found in 56%. Four died (12½%).

"Sixty-one cases of lymphocytic meningitis were studied. Having excluded 10, five due to leptospirosis

and five who have received antibiotic therapy, of the remaining 51 a definite etiological agent was found in five cases: four due to poliomyelitis and one to coxsackie B4. A possible etiological agent was found in 12 cases: seven were possibly due to mumps, four to herpes, and one to E.C.H.O.–14.

"A possible diagnosis was made in a total of 17 patients (33%). Three E.C.H.O. viruses isolated from patients with meningism without C.S.F. pleocytosis are mentioned.

"The six instances of paralytic poliomyelitis were considered definite from the point of view of diagnosis, and proved virologically in four.

"The results are discussed, comparing them with studies carried out in the United States of America, and viewing the findings in the light of the viral population of Auckland."

Appendum

"Since the time of writing, polio type III has been isolated from a further case of lymphocytic meningitis (T.F., Table IIIb)."

DEODHAR, N. S. **The Status of the Microscopic Diagnosis in the Epidemiology of Smallpox.** *Indian J. Med. Sci.* 1961, July, v. 15, No. 7, 517–28, 2 figs. on pl. [24 refs.]

The author is of the opinion that under the conditions which obtain in India the most suitable laboratory test for smallpox is the examination of smears for the characteristic elementary bodies. In support of this thesis that the smear test can be very helpful in the diagnosis of early and doubtful cases of smallpox he lists 31 such cases in which the results of the test and the final diagnosis were in agreement.

The author describes the technique which he employs in the preparation, staining and examination of the smears and the points of differentiation between smallpox and chickenpox for which he looks. For these details the original paper should be consulted.

Control slides of "typical" smallpox and chickenpox, and of smears from streptococcal and staphylococcal cultures stained with the same technique, should be available. *J. Pickford Marsden*

TUCKER, E. S., III & SCOFIELD, G. F. **Hepatoadrenal Necrosis. Fatal Systemic Herpes Simplex Infection; Review of Literature and Report of Two Cases.** *Arch. Pathology.* 1961, May, v. 71, No. 5, 538–47, 5 figs. [31 refs.]

The authors review 17 records of systemic herpes infection reported in the literature, 2 of which have been abstracted previously [this *Bulletin*, 1952, v. 27, 977 *bis*], and then describe 2 cases observed by them personally.

(1) A female infant developed a febrile illness with cyanosis on the 5th day of life and died on the 8th day. At autopsy the liver was enlarged and there were haemorrhages in the serous membranes, meninges, kidneys and adrenals, and extensive necrosis of the lower end of the oesophagus. On microscopical examination the liver showed extensive haemorrhagic necrosis, with intranuclear inclusions in the surviving cells, and inclusions were also found in the adrenals and the lesion in the oesophagus.

(2) A female child aged 18 months developed a cough with generalized rash and low-grade pyrexia, followed after 3 weeks by convulsions, tachycardia and cyanosis leading to death after 3 days. At autopsy the liver showed areas of haemorrhage and necrosis, the adrenal cortex was mottled and there was liquefaction of the mucosa at the cardio-oesophageal junction. Intranuclear inclusions were found in the lungs, liver, adrenals and oesophagus.

In neither of the cases could the inclusions be stained by standard procedures. The diagnosis of herpes infection was based entirely on autopsy findings, and by the time it had been made it was too late to take material for virological investigation. The authors draw attention to this circumstance, and suggest that a diagnosis of herpes with the necessity of virological confirmation should be borne in mind in the presence of similar autopsy findings. *D. J. Bauer*

SCHWARZ, K. **Control of Infections of the Respiratory Tract. The Possible Role of "Harmless" Infections in Childhood in the Aetiology of Respiratory Disease.** *Med. Officer.* 1961, July 28, v. 106, No. 4, 69–70, 1 fig. [11 refs.]

The author used a selective cough depressant, P-n butylaminobenzoic acid, to reduce the infective dose of virus in an institutional outbreak of mumps. He claims success and urges that such methods should not be overlooked in an attempt to control the spread of infections that are usually considered harmless although they may be aggravating factors in the aetiology of severe respiratory disease. *A. B. Christie*

GRIST, N. R., KERR, J. & ISAACS, B. **Rapid Serological Diagnosis of an Outbreak of Influenza.** *Brit. Med. J.* 1961, Aug. 12, 431.

In an individual patient with clinical influenza, a rise in specific antibody titres over the course of infection is commonly accepted in aetiological evidence. The authors have extended this line of reasoning, and their argument may be summarized thus:—

In an outbreak of clinical influenza in a community, some members will be acutely ill and others will have been ill for a longer time or convalescent; a significant difference in antibody titre for a given influenza virus between the "acute" patients and the "convalescent" patients will have the same import as that between "acute" and "convalescent" serum samples in one patient.

The reactions of a logician to this reasoning would be of interest, but in practice the application of these views to an obvious outbreak of influenzal illness in a geriatric unit was of diagnostic value.

Virus isolation studies, or conventional serological tests on paired sera from individuals, have the disadvantage of

being retrospective. By comparing serum samples all taken in one day from "short duration" and "long duration" groups of cases, a rapid presumptive diagnosis was possible; 13 of 14 patients had influenza A complement-fixing antibody, and 3 patients in the 7th or later day of illness had titres of 16, 64 and 256. In most cases there was no detectable CF antibody to influenza B or C, adenoviruses, psittacosis or *Rickettsia burneti* groups. Later tests on paired sera showed a rising titre of influenza A antibody only in all individuals.

Derek Hobson

GARDNER, P. S., WRIGHT, A. E. & HALE, J. H. **Faecal Excretion of Adenovirus in a Closed Community.** *Brit. Med. J.* 1961, Aug. 12, 424–6. [14 refs.]

This paper reports the pattern of excretion of adenoviruses found over a period of 1 year in a residential nursery of some 25 children; those under 1 year old were housed separately from children 1–6 years old.

Adenoviruses types 1–7 were all recovered from faecal samples obtained at fortnightly intervals from staff and children; type 5 was found in 88/125 specimens (69·5%) whereas the next most frequent virus, type 1, occurred in only 13·5% of specimens. In 5 children, adenovirus type 5 excretion was prolonged for periods of 3–6 months; 4 of these were infants of 1 year old or less, and 2 of these excreted other types of adenovirus at intervals during the period of carriage of type 5. The younger the child, the more likely was adenovirus excretion—20/34 (59%) of isolations were in children under 1 year compared with 13/34 (38·2%) in those aged 1–6 years and 6/21 (35%) in the adult staff.

With one exception, adenovirus excretion could not be correlated with any clinical illness in the nursery: in one episode, 4 children became ill with bronchiolitis, and all were found to have begun faecal excretion of adenovirus type 5 after the beginning of the illness.

In the authors' view the frequency and degree of faecal excretion of adenoviruses suggests multiplication within the alimentary tract, perhaps in lymphoid tissue. [An enteric phase of proliferation for certain adenovirus types is strongly suggested also by the observations of ROSS and POTTER (*Lancet*, 1961, v. i, 81) on the frequency of adenovirus isolation in acute intussusception.]

Derek Hobson

BRITISH MED. J. 1961, Sept. 2, 597–605. [13 refs.] **Poliomyelitis-Like Disease in 1959. A Combined Scottish Study.**

This most interesting and valuable study is a combined report, from the main infectious disease units in Scotland, of investigations into poliomyelitis-like disease in 1959. The value of virological and clinical studies is clearly shown.

Cases were assessed clinically and classified in 3 categories in ignorance of the virus results. Group A patients had paralysis as a prominent symptom and were clinically classified as having poliomyelitis. Group B patients were suffering from abacterial meningitis and Group C were a heterogeneous group of cases not falling into the other 2 categories. There were 13 patients with paralytic poliomyelitis. No virus infection was identified in 3 but the remaining were infected as follows: Coxsackie A7, 7; ECHO virus Frater, 1; poliovirus type 1, 1; and adenovirus type 7, 1. An aetiology was determined for 145 of 271 cases of abacterial meningitis, mainly Frater virus, Coxsackie A7 and B5. The range of clinical illness associated with the various virus infections is considered with brief case histories. Coxsackie A7 seems clearly established as a potential cause of paralysis. 1 patient died. 4 of the 7 patients had been given 2 or more doses of poliovaccine. Coxsackie A7 was also associated with abacterial meningitis in which convulsions and twitching sometimes occurred, symptoms not seen with the other agents. Coxsackie B infections occurred in 20 patients, 15 due to B5, 4 to B2 and 1 to an untyped virus. ECHO virus infections were mainly associated with abacterial meningitis and 9 types were represented (types 1, 3, 5, 6, 9, 11, 14, 15 and Frater). Cases were mainly associated with Frater virus which, like Coxsackie A7, was predominantly isolated from males but, unlike Coxsackie A7, attacked more children over 5 than under 5. The suggestion that Frater virus infection might be new to the area was supported by finding antibodies in only 9% of blood donor sera collected in 1958. Infections with mumps, herpes simplex, louping ill, adenovirus, probably lymphocytic choriomeningitis and leptospirosis were also discovered, mainly in patients with abacterial meningitis.

This study emphasizes that in any year many viral agents may be causing the syndromes of "poliomyelitis-like illnesses". This applies to paralytic as well as to non-paralytic cases. Clinical and cerebrospinal fluid analysis are unable to distinguish aetiological entities. The methods of laboratory study are important. Thus the 2 most prevalent viruses in this epidemic grow poorly or not at all in the widely used monkey kidney cells. Frater virus grows best in human thyroid cells and Coxsackie A7 in suckling mice. Approximately half the cases of aseptic meningitis did not yield a virus, presumably mainly because the wrong technique of isolation was used.

A. J. Beale

DÖMÖK, I. & MOLNÁR, Elisabeth. **Enterovirus Studies in connection with the 1959 Poliomyelitis Epidemic in Hungary.** *Acta Microbiologica.* Budapest. 1961, v. 8, No. 2, 189–203, 4 figs. [13 refs.]

Hungary experienced a severe epidemic of poliomyelitis in 1959 with an incidence of 18·3 per 100,000. Approximately one-third of the patients were examined for polioviruses and the results of these studies are reported.

Poliovirus type 1 was isolated from 74% of 625 patients with confirmed clinical poliomyelitis. Other enteroviruses were isolated in small numbers: poliovirus type 2, 2; type 3, 8; ECHO, 11; and Coxsackie, 6. 25% of the patients suspected of having poliomyelitis, but in whom the diagnosis was subsequently rejected on clinical grounds, yielded a poliovirus, whereas only 6% of the patients with abacterial meningitis and also of non-neurological diseases yielded a poliovirus. Similarly, 34%

of the contacts of patients excreted poliovirus. In a children's nursery 81% of the contacts of a poliomyelitis patient excreted type 1 poliovirus. 1 child excreted Coxsackie B2 but this virus did not spread, presumably because of interference exerted by the poliovirus.

Serological studies in a number of cases of poliomyelitis confirmed that poliovirus was probably not the cause of the disease. In some cases other enteroviruses were isolated and in some at least they may have been responsible for the disease but in no such case were paired serum samples examined. Poliovirus isolations were less common as age increased and the later the specimens were taken. The authors believe that this fact explains the failure to isolate virus from some patients with poliomyelitis. In view of the virus studies they think that some of the cases rejected on clinical grounds as not being due to poliomyelitis were probably due to the virus. The fact that abacterial meningitis was rarely due to poliovirus despite the epidemic was confirmed by a few serological results.

The authors note that a mass vaccination campaign with attenuated polioviruses was started in December 1959 and they expect that they have had the last opportunity to study a major outbreak of poliomyelitis in Hungary.

A. J. Beale

El-Messih, G. A. **The Epidemiological Pattern of Poliomyelitis in relation to Control (with reference to Experience in Egypt).** *J. Egyptian Pub. Health Ass.* 1960, v. 35, No. 3, 101–27, 6 figs.

This is a very good statement of modern views on the epidemiological patterns of poliomyelitis infection and disease in different types of country. In most tropical countries, and in Egypt, the infection is highly endemic, the population being continuously exposed to infection (both faecal and oro-pharyngeal) at all ages. Thus 90% of the paralytic cases are in the age-group 6 months to 2 years, and about 100% of the population have become immune by age 5 or so.

In countries with a high standard of hygiene, on the other hand, there is a delayed rise in serum neutralizing antibodies, and, as shown by surveys in Charleston, U.S.A. [Paul, this *Bulletin*, 1955, v. 30, 572], only 60% of the population have become naturally immune by age 15. The seasonal distribution in countries with a high standard of sanitation is in summer and autumn (a fact not yet satisfactorily explained), and in Egypt on the other hand there are two peak periods of incidence, in April-June and in September, times which correspond with the two peak breeding seasons of house-flies.

Salk vaccination has been proved beyond doubt to be highly, though not completely, efficacious in preventing paralytic poliomyelitis. In 1958, however, in U.S.A., as many as one-third of the paralysed patients had been vaccinated. The relative rise in incidence of paralysis in that year suggests either that the immunizing effect of Salk vaccination may wane after a few years, or that the community was attacked by a virus of increased virulence.

Application of such principles to Egypt suggests that no wholesale vaccination of the Egyptian population is necessary. But in view of the prospect of rising standards of hygiene with increasing industrialization in the next few years, it is suggested that infants should have 3 doses of vaccine between 2 and 6 months of age, with a booster dose in the second year of life. Thereafter it could be left to nature to give the booster doses required to maintain the immunity of the entire population.

H. Stanley Banks

Harries, J. R. & Lawes, W. E. **The Use of Light Hypothermia in Acute Life-Threatening Poliomyelitis.** *South African Med. J.* 1961, July 15, v. 35, No. 28, 573–4. [14 refs.]

The authors, from Nairobi, report the effect of hypothermia on 9 patients suffering from acute life-threatening poliomyelitis. Cooling was effected by a water bed under the patient and shivering was prevented by giving intravenous promethazine, chlorpromazine and pethidine. 3 of the 9 patients died: in all 3 cooling was allowed to go below 31°C. (88°F.). 3 patients had hyperpyrexia—a temperature of 40°C. (104°F.) for 3 to 10 days after the onset of paralysis—and all 3 survived. The authors feel that cooling should not go below 32·2°C. (90°F.) and need not be prolonged for more than 5 or 6 days. They feel that hypothermia reduced mortality in their 9 cases. [The patients were all desperately ill and to save 6 of 9 such patients is an achievement. Others who may have tried this method may be encouraged by these results and should read the article in the original.]

A. B. Christie

Chin, T. D. Y., Marine, W. M., Hall, E. C., Gravelle, C. R. & Speers, J. F. **Poliomyelitis in Des Moines, Iowa, 1959. The Influence of Salk Vaccination on the Epidemic Pattern and the Spread of the Virus in the Community.** *Amer. J. Hyg.* 1961, July, v. 74, No. 1, 67–94, 13 figs. [25 refs.]

There is an interesting and illuminating account of the Des Moines poliomyelitis outbreak in 1959. It is required reading for anyone interested in the control of poliomyelitis. There is a detailed epidemiological, clinical and virological study of the outbreak. It was severe: the attack rate of 66·5 per 100,000 has only been exceeded in 1954 (87·9) and 1952 (165·8). The disease differed strikingly from that of earlier years. Cases predominated in pre-school-age children and in the poorer centre of the city. In 1952 and 1954 the attack rate was highest in upper and middle white socio-economic groups, falling to its lowest levels in the Negroes. In 1959 the order was reversed, the Negroes experienced very high rates (320) and the lowest was in the upper white group (15·6).

The upper white group had the best record of vaccination and the Negroes the worst. The vaccine was very effective. Estimates of reduction in incidence of paralytic poliomyelitis for those under 10 years who had 3 or more doses were 92, 70 and 88% for middle white, lower white and Negro groups, respectively. Only 2 cases occurred in the vaccinated upper white group. Moreover, paralysis was less severe in vaccinated (3 doses) persons. Thus it was minor in 41% of the vaccinated and 16% of the unvaccinated.

Type 1 poliovirus was isolated or shown serologically to be responsible for 85% of the paralytic cases studied and 59% of the abacterial meningitis cases. 64 stools from abacterial meningitis subjects were examined and 22 yielded poliovirus type 1 and 11 other viruses (2 Coxsackie B2, 2 ECHO 7 and 7 unidentified). The non-polioviruses were isolated during the second wave of the epidemic in August. Poliovirus type 1 was isolated from virtually all sewage samples from the poor areas but only rarely from those from richer neighbourhoods. This suggests that Salk vaccine may have limited the community spread of poliovirus. The virus, however, was isolated as frequently from throat swabs of vaccinated as from unvaccinated people. Poliovirus type 3, ECHO 8 and unidentified viruses were also isolated.

One poliovirus was isolated from the cerebrospinal fluid [only the second reported instance of this known to the abstracter]. *A. J. Beale*

DANE, D. S.; DICK, G. W. A.; BRIGGS, Moya; NELSON, R.; MCALISTER, J.; CONNOLLY, J. H.; HAIRE, Margaret; MCKEOWN, Florence; FIELD, C. M. B. **Vaccination against Poliomyelitis with Live Virus Vaccines. 6. Changes in Sabin Type II Oral Vaccine Virus after Human Passage** [DANE, DICK, BRIGGS, NELSON, MCALISTER, CONNOLLY, HAIRE, MCKEOWN & FIELD]. *Brit. Med. J.* 1961, July 29, 259–65, 3 figs. **7. Effect of Previous Salk Vaccination on Virus Excretion** [DICK, DANE, MCALISTER, BRIGGS, NELSON & FIELD]. *Ibid.*, 266–9, 5 figs. [13 refs.] **8. Changes in Sabin Type I Oral Vaccine Virus after Multiplication in the Intestinal Tract** [DANE, DICK, BRIGGS, NELSON, MCALISTER, CONNOLLY, MCKEOWN & FIELD]. *Ibid.*, 269–71, 1 diagram.

These 3 papers describe interesting experiments carried out by Professor Dick and his colleagues in Belfast into problems associated with the use of attenuated poliovaccine [see also this *Bulletin*, 1957, v. 32, 311, *ter*; 1959, v. 34, 200, *bis*].

(6) In the first paper changes in the characters of the type 2 strain of Sabin's attenuated poliovaccine are described. The infectivity of this and of a first human passage strain were similar in that a few hundred TCD50 produced infection in about 50% of the children. The first passage virus spread to the majority of the contacts in a ward of 33 children aged 5–17 months in a children's home. Virus was excreted in high titre (10^5 TCD50 per gm. of faeces) by the majority of the children by 5–7 days. As a result of the infection good titres (well over 1 in 100) of antibody were produced.

Virus at high titre was tested for marker characters. It was found that at the time the virus was being excreted at high titre in the gut (regardless of the number of passages) the virulence for monkeys assessed both by lesions and paralysis increased. Virus in these studies was inoculated intracerebrally after one pass in monkey kidney cells. Thus, while the vaccine strains caused neither paralysis nor lesions, 9 out of 21 and 19 out of 21 monkeys, respectively, were paralysed and showed lesions after inoculation with virus passed for 5 weeks in the human gut. The lesions and the paralysis, however, differed from those caused by strains from paralysed patients in being less extensive and progressive. The passage virus resembled more relatively avirulent wild strains than fully virulent ones. Ability to multiply at different temperatures was also studied. First, a survey showed that some strains isolated from paralysed patients could not multiply at 40°C. when the temperature was carefully controlled in a waterbath, whereas all could at 39°C., a temperature inhibiting the vaccine strains. Using 39°C. as the dividing temperature the authors noted a progressive change to t+ on passage in the human gut. Similarly, a partial change from $d-$ to $d\pm$ was observed in 9 out of 12 strains of type 2 virus isolated from vaccinated persons.

Seven relatively attenuated type 2 viruses were isolated during a community surveillance programme. 3 of these patients had been in contact with vaccinated children but the rest had not. In conclusion, the authors note that no case of type 2 poliovirus occurred during or after their trial and they believe that the changes they have noted in the virulence of type 2 strains are not necessarily a hazard in the use of attenuated poliovaccine.

(7) The second paper in the present group considers whether Salk type poliovaccine can influence the spread of polioviruses. The epidemiological and chimpanzee evidence in favour of the idea that killed vaccine may limit spread, and the evidence from deliberate feeding experiments that it has no influence on virus excretion, is briefly reviewed. 2 trials are described.

In the first, groups of children aged 5–17 months were fed $10^{5\cdot6}$ TCD50 of type 2 virus but one group had previously received 2 doses of commercially available killed vaccine. No child had actively acquired antibodies before vaccination. After 2 doses of killed vaccine the geometric mean titre to type 2 was 1 in 525. No difference in geometric mean titre of virus excreted in the stools by the 2 groups was found. The proportion of infants with virus titres of 10^5 TCD50 per gm. or more was slightly lower in those with antibody titres over 1 in 1000 as a result of Salk vaccination.

In the second trial children aged 6–18 months were fed 10^6 TCD50 of Sabin's type 1 virus. 11 had no type 1 antibodies before feeding (9 unvaccinated and 2 after 2 doses of ordinary Salk vaccine). 9 had high titres in the faeces and 4 also excreted virus in the throat. 1 failed to excrete virus at all. 8 children had type 1 antibodies, 1 after Salk vaccination, 7 of them had 3 doses of Purivax [two 0·5 ml. doses are recommended as adequate for Purivax] and as a result had a geometric mean type 1 titre of 1 in 2750. The other child had 2 doses of commercial Salk vaccine and had a type 1 titre of 1 in 512. None of these children excreted virus in the throat and 3 failed to excrete virus at all. The other 5 became faecal excreters but both the titre and duration of virus excretion were much less than in the unvaccinated infants. The authors believe that pharyngeal excretion of poliovirus may well be important in the spread of the virus. Moreover, the block of this source of excretion may well account for the rather better results observed after the use of poliovaccine than could be expected from the proportion of people vaccinated.

(8) The character of the viruses isolated from children excreting type 1 poliovirus after swallowing Sabin's

vaccine or as a result of contact infection (which occurred in 3 out of 23 contacts) was determined. Using a dose of $10^{5 \cdot 8-6 \cdot 8}$ TCD50, the authors inoculated 10 passage viruses intracerebrally in monkeys. 7 out of 20 monkeys were paralysed and 16 out of 20 showed lesions. The monkey neurovirulence was unacceptably high for a vaccine virus although much less than for viruses isolated from paralysed patients. 4 out out of 10 strains tested were $d\pm$ instead of $d-$ and only 3 of 41 strains tested were $t\pm$ at 40°C., but at 39°C., of 19 strains tested, 7 were $t+$ and 11 $t\pm$. There was a tendency towards a progressive change in t character the longer the strains had been in the intestinal tract.

There was no evidence of spread of type 1 or type 2 virus in the community during these trials in Northern Ireland. An incident is recorded which makes the authors wish there was a more reliable way of tracing vaccine strains in the community if they are going to be used routinely. In the last half of 1960 there were 5 paralytic cases of type 3 poliovirus infection in Northern Ireland resulting from the importation of a type 3 case from England in July. This child came from a town in England where a trial of all 3 types of attenuated vaccine had been held earlier in the year. The authors state the opinion that the virus imported into Northern Ireland was not derived from the vaccine strain but pose the question "is that enough?". *A. J. Beale*

Goffe, A., Pollock, T. M. & Shand, F. L. **Vaccination of Adults with a British Oral Poliomyelitis Vaccine prepared from Sabin Strains.** *Brit. Med. J.* 1961, July 29, 272–4, 2 figs. [11 refs.]

This is the first account of the use of Sabin type poliovaccine manufactured in Britain (by the Wellcome Research Laboratories). 43 adults were fed the vaccine in a dose of 10^5 plaque-forming units in the order type 1 first, then 17 weeks later type 3 and 4 weeks later type 2 Testing difficulties with type 3 caused the departure from a monthly interval between doses. Pre-vaccination blood samples revealed that of 21 adults previously vaccinated with Salk vaccine, 1 lacked type 1 and 1 type 3 antibodies, whereas of 14 unvaccinated adults, 5 lacked type 1, 7 type 2 and 3 type 3 antibodies. 2 persons were triple negatives.

All those without antibody to types 1 and 3 produced antibodies and 5 out of 7 to type 2. The geometric mean titres were 1 in 34, 1 in 58 and 1 in 49, respectively, for types 1, 2 and 3. The 2 persons failing to respond to type 2 were triple negatives who were still excreting type 3 when type 2 was given without establishing infection or an antibody response. 7, 9 and 10 persons excreted poliovirus types 1, 2 and 3 respectively—for up to 3 weeks for type 1 and 2 but for up to 7 weeks for type 3. Virus excretion was usually accompanied by an antibody response. The geometric mean titre of antibody also rose in those who did not excrete virus. Virus excretion was much less frequent in those with antibodies and increasingly rare as the pre-vaccination titre increased.

Pharyngeal excretion rates are not reported but 1 person who complained of sore throat yielded type 1 virus from it. *A. J. Beale*

Žácek, K., Vonka, V. & Adam, E. **The Antibody Response in Children vaccinated with a) Live Attenuated Polioviruses (Sabin) and b) the Fourth Dose of Inactivated Poliovaccine.** *J. Hyg., Epidemiol., Microbiol. & Immunol.* Prague. 1961, v. 5, No. 2, 178–88.

The responses of children in Czechoslovakia to a 4th dose of inactivated poliovaccine or to live attenuated polioviruses are compared. The children receiving a 4th dose of killed poliovaccine had previously received 3 intradermal doses. Whereas, after administration of Sabin's strains, 95%, 93% and 94% responded to types 1, 2 and 3, respectively, the response to a 4th dose of killed poliovaccine was far inferior. The overall rate was 50%, 67% and 83% for the 3 types of poliovirus. However, the results were much worse in children who lacked antibodies to all 3 types of poliovirus. The relatively good overall figures were biased by the fact that many of the children had type 2 antibodies and these children made a much better response to type 1 or type 3 than children without type 2 antibodies. The authors ascribe the relatively poor response to the 4th dose of killed poliovaccine to the fact that the individuals lacked antibodies and did not make a booster response so that the 4th dose was in reality a 1st dose in a new primary course. They consider that with killed poliovaccines of the present potency it would be desirable to give 2 primary doses each year until such time as either naturally acquired infection or deliberate administration of Sabin's strains cause higher levels of antibody to be formed as a result of infection. *A. J. Beale*

Kátay, A. A poliomyelitis elleni védekezés Magyarországon. [**Measures against Poliomyelitis in Hungary**] *Népegészségügy.* Budapest. 1960, Dec., v. 41, No. 12, 341–8, 371, 2 charts. German summary.

The incidence of poliomyelitis in Hungary has increased in recent years, from a mean morbidity of 4·5 per 100,000 in 1931–50 to 9·4 per 100,000 for 1952–59; in 1957 there were 2,334 recognized cases (23·8 per 100,000), and 1,830 (18·3 per 100,000) in 1959. The high incidence in the latter years occurred in spite of the fact that 26% of the population of Hungary had received 3 injections of Salk vaccine over the same period. Towards the end of 1959 Sabin vaccine was brought into use. Trivalent vaccine was given to 195,036 persons mainly aged up to 14 years living in the province of Györ-Sopron, where the incidence of the disease was high. In the remainder of the country 2,409,011 children aged up to 14 years presented themselves for type 1 vaccine, 2,459,791 for type 2 and 2,474,420 for type 3 vaccine, as a result of which 92·4% of the total age-group were covered by vaccination. In the 6 months of 1960 following the completion of the vaccination programme 38 cases of poliomyelitis were notified. Strains of virus isolated from these patients were mainly type 1 and possessed the T-marker, and were thus in all probability wild strains.

D. J. Bauer

MESROBEANU, I., CAJAL, N. & ARION, R. Din rezultatele vaccinării antipoliomielitice cu virus viu atenuat în U.R.S.S. **[Results obtained in Antipoliomyelitis Vaccination with Attenuated Live Virus in the U.S.S.R.]** *Microbiol., Parazitol., Epidemiol.* Bucharest. 1961, Mar.–Apr., v. 6, No. 2, 97–102.

The authors give a general account of the progress of large-scale vaccination against poliomyelitis with the live attenuated Sabin strains carried out in the Soviet Union and associated countries. The Academy of Medical Sciences of the U.S.S.R. began to produce the vaccine in 1958, and by the end of 1959 enough had been manufactured to provide a course of 3 doses for 40,000,000 persons. In spring 1959 the vaccine was given to 3,500,000 persons aged from 2 months to 20 years in the Baltic countries, White Russia and elsewhere. In the second half of the year 15,200,000 persons were vaccinated in various parts of the Soviet Union among a total population of 65,000,000 in the areas concerned, and also 2,300,000 in Hungary, 40,000 in Bulgaria, 3,000 in Peking and 50,000 in Viet-Nam. In 1960 the number of persons who had received Sabin vaccine reached 85,000,000. By vaccinating entire populations simultaneously it was hoped to avoid the appearance and spread of variants of the virus with increased neuropathogenicity. No case of poliomyelitis due to the vaccine virus was observed in the Soviet Union. An epidemic of poliomyelitis which ocurred in Tashkent in 1959 came to an abrupt end after 370,000 inhabitants had been given the live vaccine. *D. J. Bauer*

SABIN, A. B., MICHAELS, R. H., SPIGLAND, Ilya, PELON, W., RHIM, J. S. & WEHR, R. E. **Community-Wide Use of Oral Poliovirus Vaccine. Effectiveness of the Cincinnati Program.** *Amer. J. Dis. Children.* 1961, May, v. 101, No. 5, 646–67. [21 refs.]

Sabin believes that the extensive use of attenuated poliovaccine may not only prevent the disease poliomyelitis but also eliminate the causative poliovirus, thus eradicating the disease completely. In this paper the first extensive community-wide use of his vaccine in the U.S.A. is described.

This is a most impressive study. The vaccine used was monovalent given in the order type 1, 3 and 2, employing 2×10^5, 3×10^5 and 1×10^5 PFU for types 1, 2 and 3 repectively, with 1 month's interval between types. 6 weeks is considered an optimal interval to establish good alimentary immunity but insufficient time was available in Cincinnati as the programme did not start until April 1960. Vaccine was given in syrup and a warning is sounded that some preparations of commercially available syrup destroyed the virus very rapidly. The vaccine was given to 76·7% of the children aged from 3 months to 18 years in Cincinnati, 73% of those 3 months to 5 years. Obviously ill or febrile children were not vaccinated in case they might harbour an interfering virus or be incubating poliomyelitis. There are no other contra-indications but in Cincinnati children who had had tonsils or adenoids removed recently were not vaccinated and it was recomended that such operations should not be performed. This recommendation was disregarded without untoward result. Children were vaccinated regardless of their Salk immunization status. 73% of the predominantly middle and upper income-group children had had 3 or more doses but only 34% of those from the poorest neighbourhoods. The parents had often not had any doses of Salk vaccine (46% and 24·5% of the fathers and mothers of pre-school children respectively). The proportions of higher income group children between the ages of 7 months and 2 years lacking antibodies despite a full course of Salk vaccination were 43%, 30% and 29% for types 1, 2 and 3 respectively.

The response to oral vaccine was excellent. Only 2 out of 19 triple negatives failed to produce antibodies to a titre of more than 1 in 8 against all 3 types. There was 1 type 1 and 1 type 3 failure but the majority of the titres were over 1 in 100. Evidence of spread of virus from pre-school children to school-children in contact was obtained. The community spread of enteroviruses increased to a peak in September but for polioviruses declined rapidly to low levels after the completion of administration of vaccine. During the surveillance 57 cases were investigated, 31 in vaccinated and 26 in unvaccinated people. Only 1 case of proven paralytic poliomyelitis (due to type 1 virus) occurred. This was in an unmarried man of 25 who became paralysed within 13 days of returning to Cincinnati from 2 months in Massachusetts. He was considered to have been infected outside the area. Cases of ECHO 6 and 18 and Coxsackie B4 encephalitis in vaccinated persons occurred.

[This paper is required reading by those concerned with poliomyelitis prevention.] *A. J. Beale*

WIESENER, H., LENNARTZ, H. & ENDERS-RUCKLE, G. Poliomyelitisschutzimpfung mit abgeschwächten Viren. **[Immunization against Poliomyelitis with Attenuated Live Virus]** *Deut. med. Woch.* 1961, June 2, v. 86, No. 22, 1084–8, 1120, 2 figs. [14 refs.]

In 1960 vaccination with live trivalent attenuated poliomyelitis vaccine of Cox type was carried out on 279,914 children and adults aged from 3 months to 40 years living in West Berlin, and 139 vaccinated infants and children resident in 3 institutions were subjected to serological and virological study.

Among 55 children aged up to 2 years serological conversion rates of 88% and 100% to types 1 and 3 were observed, with mean post-vaccination titres of 512, but the response to type 2 was less satisfactory (40% conversion and mean titre of 16). Similar results were observed in 78 children aged 2–10 years, who showed conversion rates of 80%, 68% and 96% and mean titres of 512, 128 and 512 for the 3 types respectively. Among 48 triply negative children, 40 of whom were under 2 years of age, 16 developed antibody to all 3 types as the result of vaccination, 27 to types 1 and 3, 1 to types 2 and 3, 3 to type 3 only, and 1 failed to develop antibody. Virus of types 1 and 3 were recovered from the stools in many instances after vaccination, but type 2 virus was isolated only rarely.

After the vaccination campaign 55 persons in West Berlin developed poliomyelitis in the remaining part of the season, of whom 17 had been vaccinated.

D. J. Bauer

De Sanctis-Monaldi, T., Lippi, M., Sebastiani, A. & Frugoni, G. Stato attuale della vaccino-profilassi antipoliomielitica (con contributo sperimentale). **[The Present State of Immunization against Poliomyelitis (with an Experimental Contribution)]** *Arch. Ital. Sci. Med. Trop. e Parassit.* 1961, Apr. & May, v. 42, Nos. 4 & 5, 157–97; 231–61, 1 diagram. [227 refs.] English summary (7 lines).

The authors report on their laboratory findings in 21 cases of poliomyelitis which involved Rome children who had been previously given a course of Salk vaccine. They isolated type 1 virus from the faeces of 12 and type 3 from one other.

In the winter of 1960, in a Rome convalescent home where many children were recovering from non-pulmonary tuberculosis, the writers of this paper administered a Cox form of a live trivalent vaccine by mouth to 80 of these children and also to 16 adult volunteers. The children had already received a course of 2–3 doses of Salk vaccine some months before. In a preliminary investigation, 8 out of 32 of the children and none of the adults were found to be serum-negative against all 3 types of the poliovirus. After taking the live virus, one only of these 8 children remained serum-negative to all 3 types. 7 of 10 children who had been found serum-negative for type 1, 7 of 13 negative for type 2 and 10 of 12 negative for type 3 were found to have converted after the oral administration of attenuated live vaccine. This raised the antibody titre at least 4-fold in about half the subjects. The conversion rate was much less impressive in the adults. No clinical reactions of any sort followed the vaccination with this live virus.

In the following summer the authors investigated 31 children, aged 1½–3 years, in one of the wards. All were recovering from non-pulmonary tuberculosis, were free from fever and had already been immunized with Salk vaccine—2–3 doses. 8 had also received Cox's vaccine by mouth 5 months before, with good serological results. 6 were now given a dose of Cox's attenuated type 3 strain and this virus appeared in the faeces of 2. The other 25 children in the ward, who were contacts, were followed-up and only one was found to have acquired and to excrete the virus.

The paper includes a good account of the literature as well as indicating the techniques and discussing the findings of the authors. *J. Cauchi*

Levine, Sonnia, Goldblum, N. & Friedman, E. **Virologic Findings and Antibody Response of Newborns fed Multiple Type Oral Poliomyelitis Vaccine.** *Amer. J. Hyg.* 1961, July, v. 74, No. 1, 95–103, 1 fig. [14 refs.]

The immunization of newborn children against poliomyelitis has great administrative advantages. Therefore 53 newborn infants in Israel were fed trivalent attenuated poliovaccine (Cox's strains containing the following TCD50: type 1, $10^{5\cdot7}$; type 2, $10^{4\cdot2}$; type 3, $10^{6\cdot2}$) at 3 to 5 days and again at 2 months old. 10 in the first test and 28 on refeeding failed to excrete virus. At 3 to 5 days 31 infants excreted types 1+3 and 6 type 1 and 6 type 3 only. Small numbers excreted every possible combination of types on refeeding.

The response to vaccine was estimated at 6 months. 88% and 98%, respectively, had titres in the range 1 in 16 to 1 in 256 to types 1 and 3, whereas only 11% had such titres to type 2. Thus, for type 2 there was a fall in titre with age as passively acquired antibodies disappeared, whereas for types 1 and 3 the distributions of antibody titres at birth and at 6 months were closely similar. Excretion of virus was not necessary for an antibody response, especially for type 3 poliovirus.

Some evidence for interference by wild enteroviruses at 2 months but not at 3 to 5 days was found.

A. J. Beale

Plotkin, S. A., Lebrun, A., Courtois, G. & Koprowski, H. **Vaccination with the CHAT Strain of Type 1 Attenuated Poliomyelitis Virus in Léopoldville, Congo. 3. Safety and Efficacy during the First 21 Months of Study.** *Bull. World Health Organization.* Geneva. 1961, v. 24, No. 6, 785–92.

Between August 1958 and April 1960 some 75,000 African children under the age of 5 years were vaccinated with the CHAT type 1 strain. In the age-group 6 months to 2 years, in which most cases of poliomyelitis occur, 41,400 children were vaccinated out of a total of some 46,200. Since the beginning of the campaign 39 attacks of paralytic poliomyelitis have occurred in vaccinated individuals. Only 5 of these attacks had an onset within 2 months of vaccination and at current attack rates it is estimated that 8 cases might have been normally expected in the absence of vaccination. In other words there is no evidence of infection from the vaccine. Serological evidence also supports its safety. From a calculation of the person-weeks of exposure in vaccinated and unvaccinated groups it is estimated that the attack rate of paralytic poliomyelitis in the vaccinated children aged 6 months to 2 years was only one-third the attack rate in the unvaccinated. It is also noted that in mid-1959 there was a shift in Léopoldville from type 1 to type 3 as the predominant cause of paralytic poliomyelitis. This might be due to 3 factors—chance, an exhaustion of type 1 susceptibles in the 1958–59 epidemic, or the reduction through vaccination of the circulation of wild type 1 virus. Probably all 3 factors played some part and it is not possible to assess the relative importance of vaccination. Unfortunately the political situation has prevented any continuation of these observations.

[For parts I and II, see this *Bulletin*, 1960, v. 35, 794.]

Austin Bradford Hill

Ulrich, J. & Novák, M. Epidemický výskyt akutní benigní perikarditidy. **[Epidemic Occurrence of Benign Pericarditis]** *Časopis Lékařů Českých.* Prague. 1961, Mar. 17, v. 100, No. 11, 330–35, 1 graph & 1 fig. [36 refs.] English summary (9 lines).

In 1958 the authors observed 5 cases of acute benign pericarditis which occurred in the Most district of Czechoslovakia at the same time as an epidemic of an acute febrile illness of Coxsackie type characterized by

muscle pains and prostration. 5 case histories are given in illustration. In 4 patients the heart condition supervened upon febrile upper respiratory catarrh, and in the other the illness began with abdominal pain simulating acute appendicitis. Substernal pain developed with pericardial friction lasting 3–10 days. Electrocardiographic changes characteristic of acute pericarditis were observed. The course was benign, with complete recovery. *D. J. Bauer*

MARCHESSAULT, V., PAVILANIS, V., PODOSKI, M. O. & CLODE, M. **An Epidemic of Aseptic Meningitis caused by Coxsackie B Type 2 Virus.** *Canadian Med. Ass. J.* 1961, July 15, v. 85, No. 3, 123–6, 1 fig. [15 refs.]

This is a report of an outbreak of abacterial meningitis, involving 61 patients admitted to Montreal Children's Hospital between late June and early October 1960. In 55 of the 61 Coxsackie virus B2 was isolated from the faeces: in the remaining 6 patients a significant rise in serum antibodies occurred. Along with symptoms of meningitis a feature of the outbreak was the occurrence of abdominal and sometimes chest pain and a vesicular form of pharyngitis in almost half the patients.
A. B. Christie

GIORN. DI MALATTIE INFETTIVE E PARASSIT. 1960, Sept.–Oct., v. 12, Nos. 9/10, 464–524, illustrated. [Numerous refs.] La epatiti infettive. **[Infective Hepatitis]** [Papers presented at 2nd International Congress of Infective Pathology, Milan, 6–10 May 1959.]

At the Second International Congress of Infective Pathology held in Milan in 1959 part of the proceedings was devoted to a consideration of infective forms of hepatitis. 21 papers were presented, only a few of which can be mentioned within the limits of the present review. An account of the clinical and epidemiological aspects of infective hepatitis was given by F. RUSSI (p. 469–472). Between 1950 and 1958, 559 cases with this diagnosis were observed; 57% were in children below 15 years of age, and 148 were in adults. The mortalities in children and adults were 1·54% and 4·43% respectively, and the mean durations of hospital treatment were 14 and 34 days. 44 patients (29%) were considered to be suffering from inoculation hepatitis.

The comparative incidence of infective hepatitis and enteric infections is discussed by N. CONSTANTINESCO, O. ZAVATE, N. BIRZU, C. BERCOVICI, C. OANER and S. FREUND (pp. 470–482). The figures for 11 towns in Rumania between 1953 and 1957 show that the annual incidence is around 400 per 100,000, with no essential difference between adults and children. Between 1955 and 1958 epidemic waves of dysentery and enteritis were observed each year in the summer, whereas typhoid occurred only rarely. In observations carried out in residential communities of children it was noted that epidemics of dysentery, varicella or measles did not favour the development of epidemic foci of infective hepatitis, and in groups of adults, 1 of which contained 3,000 persons no relationship was observed between the incidence of infective hepatitis and the occurrence of epidemics of dysentery and enteritis. It thus appears that infective hepatitis is transmitted among the population by a route which differs from that of the enteric infections.

The views of the Rumanian school on the nature of infective hepatitis virus are put forward by S. S. NICOLAU and N. CAJAL (pp. 486–491). An extensive epidemic of the disease occurred in Rumania in 1941–44, after which the disease subsided, to be followed by a new outbreak in 1948, which has continued up to the present time. The appearance of the liver in these latter cases differs from the classical picture of infective hepatitis in the abundance of connective tissue, which proliferates to such an extent as to replace four-fifths of the parenchyma, and also in the absence of intranuclear inclusions. To explain these differences Nicolau and his collaborators postulate the existence of a variant of infective hepatitis virus which gives rise to a disease which they call sclerogenous hepatitis. Haemagglutination could be obtained with fragments of liver from patients with infective hepatitis; it was ascribed to the presence of the virus and could be inhibited by specific immune serum. Since the second half of 1954, however, a further variant of the virus has arisen which no longer possesses the power of causing haemagglutination.

The epidemiology of infective hepatitis in Rumania since 1948 possesses a number of peculiar features, which are described in a further paper by S. S. NICOLAU, S. BIBERI-MORIANU and N. CAJAL (pp. 492–499). The peak in the incidence occurred at first in the spring-summer period rather than in autumn, and the morbidity has been increasing each year. The increase is a true one and cannot be ascribed solely to greater efficiency in notification; it has taken place in spite of public health measures, and has not been paralleled by a similar rise in the incidence of any other infectious disease. Infective hepatitis is mainly confined to industrial centres and affects adults rather than children; it is losing its seasonal periodicity and the peaks of increased incidence have become much less marked.

The epidemiology of the disease in Czechoslovakia is described by K. RASKA and J. RADKOVSKÝ (pp. 514–522). Cases have been recorded and followed up between 1950 and 1958 in 10 districts of Czechoslovakia. The morbidity in Bohemia and Moravia was 500 per 100,000 in the winter of 1950–51, but did not attain this level in Slovakia until 1954. The mean morbidity over the whole period was 272 per 100,000 in the Czech districts and 200 per 100,000 in Slovakia; the figure for poliomyelitis over the same period was 63·2 cases per 100,000, and the ratio between manifest cases of infective hepatitis and poliomyelitis was 42·1.
D. J. Bauer

DAVIES, A. M. & SUCHOWOLSKI, A. **The Epidemiology of Infectious Hepatitis in Israel.** *J. Hygiene.* 1961, Mar., v. 59, No. 1, 123–32, 7 figs. [19 refs.]

Infectious hepatitis has long been known to be endemic in the Middle East, with a relatively low incidence among

the indigenous inhabitants and outbreaks among incomers. The waves of immigrants into Israel since 1947 were followed, within a year or two, by increases of incidence of the disease, particularly among immigrant children regardless of the country of origin. The notification rates during the period 1949–57 have fluctuated between 5·7 and 11·4 per 10,000, but the true incidence, as shown by reports of the Workers' Sick Fund, was probably 3 or 4 times greater. Mortality was very low (as would be expected when children mainly were attacked). The highest attack rates were in farms, agricultural schools, new immigrant towns, and communal settlements, and the peak period of incidence was in winter, as in the Western world.

The authors consider that these facts suggest a contact-respiratory form of spread. *H. Stanley Banks*

RINDGE, Mila E. **Infectious Hepatitis and its Relation to Polluted Shellfish.** *Connecticut Health Bull.* 1961, July, v. 75, No. 7, 217–22.

The author is Chief of the Epidemiology Section in the State of Connecticut, where 279 cases of infectious hepatitis were notified in the first 5 months of 1961, compared with 98 for the corresponding period, and 258 for the whole, of the year before. The incidence in the whole country (U.S.A.) for the first 20 weeks of the year was 15,773 in 1960 and 35,334 in 1961. This means that a vastly increased amount of virus is now being distributed through the sewage disposal systems with the faeces, and some of this will be finding its way to waters which bear shellfish.

In this paper, certain epidemiological data for the City of New Haven, Connecticut, are shown separately from similar data referring to the rest of the State. The history of the cases and the age, sex and seasonable distribution suggest exposure and contact infection in a majority of the city patients: in the rest of the State, the corresponding data from a substantial proportion of the patients investigated point to the consumption of oysters or clams as the cause of the illness. Investigation was continuing in efforts to learn more about the source, in or outside the State, of the incriminated shellfish, but it is known that 13 patients had eaten clams taken (not bought) from Greenwich waters. An area of these waters is known to be polluted and is not open to clamming except for the purpose of obtaining bait; notices are posted to warn the public but some people do take home the clams and eat them.

Half of 154 patients notified in Jackson County, Mississippi, and in Mobile and Pike Counties, Alabama, had recently consumed oysters from the Pascagoula River, taken about a mile downstream from the city sewage outfall. Most patients had no history of contact with a previous case.

The State of New Jersey had 800, widely scattered, cases in the first 4 months of 1961. Many of the patients showed evidence of having eaten raw clams from Raritan Bay. Samples of these waters showed bacteriological counts in excess of recommended limits and the Bay was closed for clamming on May 1, 1961. *J. Cauchi*

WEINBACH, R.; MOLDOVAN, N.; STERESCO, P. L'agglutination des hématies d'homme, formolées et tannées, par les sérums humains (agglutination HFT). Note I. Description de la méthode, définition de "l'unité hémagglutinante conventionnelle" (UHc) et interprétation statistique des résultats obtenus avec 55 sérums normaux [**The Agglutination of Tanned Formolized Human Erythrocytes by Human Sera (TFE-Agglutination). I. Description of the Method, Definition of a "Conventional Haemagglutinating Unit" (CHU) and Statistical Processing of the Results obtained by testing 55 Normal Human Sera**] [WEINBACH]. *Arch. Roumaines Path. Expér. et Microbiol.* 1961, June, v. 20, No. 2, 239–48, 1 fig. [10 refs.] Note II. L'applicabilité du test HFT en vue de la sélection objective des donneurs de sang, capables de transmettre l'hépatite virotique [**II. Applicability of the TFE-Test to the Objective Selection of Blood Donors who might transmit Viral Hepatitis**] [WEINBACH, MOLDOVAN & STERESCO]. *Ibid.*, 249–56, 1 graph. [24 refs.]

I. The first of these papers confirms that human sera will agglutinate formolized and tanned human erythrocytes (independently of blood group), defines the conditions under which reproducible and accurate titration of this activity can be made, and adopts a method of expressing the titre in *unités hémagglutinantes conventionelles* (UHC). In 55 healthy subjects, the modal UHC in the serum was between 5 and 6. and the value remained constant over 3 months in one individual. Values above 10 were considered, on adequate mathematical grounds, to be outside the normal range. In 8 subjects with viral hepatitis the mean titre was 13·46 UHC, a significant elevation.

II. The second paper explores the use of the test in the exclusion of infectious blood from use in blood transfusion. 44 patients with infective hepatitis were studied. Positive reactions were noticed to be common early in the infection, and to become negative 9 to 12 days after the onset of jaundice. Such early reactions are unlikely to be due to the presence of antibody, and in fact correspond to the time of viraemia. The authors admit that there are serological reactions common to hepatitis, glandular fever, and yellow fever, and they do not claim that their test is specific, but they think it sufficiently useful to detect viraemic blood before transfusion. *Alan B. Raper*

KLUGMAN, H. B. **Neurological Manifestations of Infectious Hepatitis. A Case Report.** *South African Med. J.* 1961, Aug. 19, v. 35, No. 33, 681–2.

"A case of infectious hepatitis with neurological manifestations is described. Recovery was complete. The literature on the subject is briefly reviewed."

[See this *Bulletin*, 1946, v. 21, 84; 1948, v. 23, 309.]

ŘEHÁCEK, J., NOSEK, J. & GRESÍKOVÁ, M. **Study of the Relation of the Green Lizard (*Lacerta viridis* Laur.) to Natural Foci of Tick-Borne Encephalitis.** *J. Hyg., Epidemiol., Microbiol. & Immunol.* Prague. 1961, v. 5, No. 3, 366–72, 1 fig.

The authors conclude that this lizard is not a reservoir of this virus.

ROSS, Constance A. C., with the technical assistance of Catherine H. GOURLAY. **Louping-Ill in the West of Scotland.** *Lancet.* 1961, Sept. 2, 527–8. [17 refs.]

" Sera from 408 patients in the west of Scotland suffering from either aseptic meningitis, encephalitis, or meningo-encephalitis, or from ' paralytic poliomyelitis ', during the two-year period, 1959–60, were examined for louping-ill antibodies by complement fixation using a mouse brain antigen.

" Only one patient, a sheep farmer with meningo-encephalitis, showed evidence of louping-ill infection.

" During the period of study, louping-ill was a serious disease of sheep in part of this area. Thus, it appears that in Scotland natural infection of man with involvement of the central nervous system is rare."

LIVANOVA, L. V. & RIAZANTSEVA, N. Y. **Clinico-Virological Parallels in Measles.** *Problems of Virology.* London. 1960, v. 5, No. 4, 493–9, 3 figs. [Translated from Russian.]

The authors studied the circulation of measles virus in 57 susceptible children vaccinated with a live measles virus vaccine, using the AVB test (agglutination of virus-coated bacteria; SERGIYEV *et al., J. Mikrobiol., Epidemiol. & Immunobiol.*, 1945, v. 3, 14) for the detection of the virus. Viraemia was detected by this method in all the children, appearing before the 4th day after vaccination in 39 and before the 8th day in 11; it was also observed in all of 28 children in contact with those who had been vaccinated. The use of the vaccine did not prevent some of the children [number not stated] from developing typical measles after exposure.

D. J. Bauer

ZIEGRA, S. R. **Corticosteroid Treatment for Measles Encephalitis.** *J. Pediatrics.* St. Louis. 1961, Sept., v. 59, No. 3, 322–3.

" The effectiveness of corticosteroid therapy in measles encephalitis was observed in a clinical study of 38 patients; 32 of these comprised a controlled study group.

" There was no apparent benefit related to corticosteroid therapy.

" There were 2 deaths; each of these patients received corticosteroid therapy."

PITT, D. B., with the collaboration of I. C. LEWIS, E. SIMS, L. DODS, N. ANDERSON & R. WALL. **Congenital Malformations and Maternal Rubella: Progress Report.** *Med. J. Australia.* 1961, June 17, v. 1, No. 24, 881–90, 4 figs. [19 refs.]

(L.485)

After a clear review of the literature, the author descrices the Australian study which was begun in 1956 and in which general practitioners and obstetricians throughout the country were asked to report cases of rubella in pregnancy to the University of Melbourne. Steps were specially taken to confirm the diagnosis and a second opinion was obtained in over half of the reported cases. After rejection of cases in which the diagnosis was in doubt there were 145 for study. 61 of these occurred in the first trimester and in 14 of these the pregnancy was terminated. In a further 14 cases spontaneous abortion occurred, an incidence of 11·4%. As a rate of 10·5% has been recorded by the same author in a study of 130 mothers of normal children it does not appear that maternal rubella promotes spontaneous abortion.

18 infants had major defects, 14 with typical rubella embryopathy. 89 were apparently normal though, with ages varying from only 8 months to 4 years, further follow-up may yet reveal some undetected cases of deafness. The distribution in time of the cases of rubella embryopathy shows that such damage is not confined to epidemics [this *Bulletin*, 1960, v. 35, 798], there being 4 cases occurring between epidemic peaks.

The mean maternal age of the women attacked by rubella was 26 years and their mean family size 2·9, figures which do not differ materially from those of a normal unattacked group, nor from those of the group with seriously affected babies.

The clinical features of the rubella were similar in the affected and unaffected groups and nothing was found to suggest the presence in the affected of either a more severe or a different type of exanthematous disease.

Of 53 mothers so far questioned only 2 admitted to severe anxiety during the pregnancy.

At different stages of pregnancy the risks of a rubella embryopathy in this series resemble very closely the figures published by Bradford HILL *et al.* [this *Bulletin*, 1958, v. 33, 551] and the Australian author brings them together in the following table:—

Combined Risks—Bradford Hill and Pitt

Gestation Period[1]	Bradford Hill		This series		Risk (Both series)
	Total cases	Affected children	Total cases	Affected children	
1st to 4th week	12	6	5	3	52·8%
5th to 8th week	20	5	12	5	31·3%
9th to 12th week	18	3	33	5	15·7%
13th to 16th week	18	2	37	1	5·5%
17th to 24th week	17	1	17	0	2·9%

[1] Calculated from 1st day of last menstrual period.

The commonest conditions were deafness, congenital heart defects and eye defects (in that order) and the majority are wholly or partly amenable to modern medical treatment. Maternal rubella is an uncommon cause of mental deficiency and only 1 case (1·6%) was found in this series.

A final report will be made in about 2 years.

[This gives an excellent account of a major contribution to this problem.]

[See also this *Bulletin*, 1957, v. 32, 724.]

Austin Bradford Hill

E

FUTTERWEIT, W. **Serum Alkaline Phosphatase Activity in Infectious Mononucleosis. A Clinical Study of Fifty-Five Cases.** *Arch. Intern. Med.* 1961, Aug., v. 108, No. 2, 253–68. [122 refs.]

"The results of the clinical and laboratory studies of 55 patients with infectious mononucleosis are presented and discussed. These observations indicate the predominance of abnormal liver function in this disease. Serum alkaline phosphatase activity was found to be increased in 80% of patients tested during the acute phase of illness. Thirteen of the nonicteric patients demonstrated a serum alkaline phosphatase and bilirubin dissociation. Correlative studies revealed a higher incidence of hepatomegaly, atypical lymphocytes, and generally a more prolonged duration of illness in these patients. Some of the implications of the elevated alkaline phosphatase levels are reviewed and discussed. With more clinico-pathologic biopsy studies will come a better evaluation of the significance and limitations of the use of this enzyme as an indicator of hepatic impairment and of prognosis in this disease."

SCHUMACHER, H. R. **Infectious Mononucleosis complicated by Chronic Thrombocytopenia.** *J. Amer. Med. Ass.* 1961, Aug. 19, v. 177, No. 7, 515–16.

ROSENFELD, M. **Cat-Scratch Disease in Two Brothers.** *Practitioner.* 1961, Sept., v. 187, No. 1119, 358–60, 2 figs.

Bacteriology and Immunity

The order in this section is:—**General; Bacteriostatic and Bactericidal Substances; Bacteria; Rickettsiae; Bacteriophages; Viruses; Immunity.**

Abstracts of papers relating to the bacteriology of plague, cholera, yaws, leprosy and certain other tropical bacterial diseases; of the rickettsial fevers; and of yellow fever, dengue, rabies and certain other tropical virus infections, are published in the TROPICAL DISEASES BULLETIN. *Their titles and page references are cited below in the appropriate sub-divisions of this section.*

GENERAL

COOK, E. B. M. **Safety in the Public Health Laboratory.** *Pub. Health Rep.* Wash. 1961, Jan., v. 76, No. 1, 51–6.

In view of the risks of laboratory infections in the procedures carried out in public health laboratories the Texas State Department of Health set up a committee to study questions of safety in laboratories in which pathogenic organisms are handled. The result of a survey carried out in 1950 has been published earlier [this *Bulletin*, 1952, v. 27, 74] and in the present paper the author presents the results of a further survey covering the period up to 1960. The recorded accidents are presented in detail in a table, and include a nearly fatal case of typhoid due to aspiration of a highly virulent strain of *Salmonella typhi* from a pipette in 1944, a fatal case of rabies contracted by a worker engaged in banding bats in caves, an infection with vaccinia virus which was in danger of involving the eye, and 2 severe cases of typhus contracted by inhaling an infected aerosol. During a survey carried out in 1960 it was noted that a number of accidents leading to laboratory infections had nevertheless occurred in a new building which was adequately designed for safely handling pathogens and the importance of constant alertness on the part of the laboratory worker is stressed. *D. J. Bauer*

WOLF, H. W., SKALIY, P., HALL, L. B., HARRIS, M. M., DECKER, H. M., BUCHANAN, L. M. & DAHLGREN, C. M. **Sampling Microbiological Aerosols.** *Pub. Health Service Publication No. 686. Pub. Health Monograph. No. 60.* Wash. 1959, Apr., pp. v + 53, 51 figs. [82 refs.]

The greater part of this useful monograph is given to brief descriptions, with illustrations and summarized technical data, of nearly 40 different bacteriological air samplers. In addition there is a general description of the principles followed in the design of bacteriological air samplers and of their respective advantages and disadvantages. Particle sizing samplers are mentioned [but the monograph was prepared before the publication of LIDWELL's description of his elegant 4-stage particle sizing slit-sampler (this *Bulletin*, 1959, v. 34, 921)]. There is a brief section on operational methods. Most of the samplers have been noted in this *Bulletin* at the time of their description. *R. E. O. Williams*

SALTON, M. R. J. **The Anatomy of the Bacterial Surface.** *Bact. Reviews.* 1961, June, v. 25, No. 2, 77–99, 12 figs. [130 refs.]

DUBOS, R. J. & SCHAEDLER, R. W. **The Effect of Bacterial Endotoxins on the Water Intake and Body Weight of Mice.** *J. Exper. Med.* 1961, May 1, v. 113, No. 5, 921–34, 4 figs.

BACTERIOSTATIC AND BACTERICIDAL SUBSTANCES; DISINFECTION

The order in this section is:—**General; Antibiotics; Colicines; other Therapeutic Substances; Disinfection.**

NYHAN, W. L. **Toxicity of Drugs in the Neonatal Period.** *J. Pediatrics.* St. Louis. 1961, July, v. 59, No. 1, 1–20, 6 figs. [108 refs.]

This paper is a review of the effects of drugs in the newborn in so far as they differ from those in the adult. It concludes with a plea for further study in this field, and even suggests that manufacturers of new drugs should be required to verify their lack of toxicity in the very young as well as in the mature. Exceptional effects of drugs in the newborn are classified according to their mechanism. The toxicity of chloramphenicol is due to the lack of necessary enzymes for glucuronidation: the same mechanism would affect acetanilide, morphine and possibly progesterone. Deficiency of renal excretion leads to high sulphonamide blood levels, and these in turn by displacing bilirubin from its binding site on plasma albumin can lead to kernicterus. Other effects are due to greater permeability (*e.g.*, of the choroid plexus) or to simple greater susceptibility of a particular immature tissue to the action of a drug. There is some discussion of how to calculate the appropriate dose for an infant from that for the adult, with perhaps some preference for a calculation based on body weight rather than surface area, but with strong emphasis on the exceptional effects to be guarded against in the neonatal period as distinct from those in the more mature infant.

L. P. Garrod

LISCHNER, H., SELIGMAN, S. J., KRAMMER, A. & PARMELEE, A. H., Jr. **An Outbreak of Neonatal Deaths among Term Infants associated with Administration of Chloramphenicol.** *J. Pediatrics.* St. Louis. 1961, July, v. 59, No. 1, 21–34, 3 figs. [41 refs.]

This report from Los Angeles deals with another "outbreak" of neonatal deaths due to chloramphenicol poisoning. All 9 occurred in the same unit during March and April 1958: apparently some obscure infection was suspected and the dose of the antibiotic was actually increased in an endeavour to overcome it. All the infants were given more, and some considerably more than 100 mgm. per kgm. daily, and died with the now familiar features of sudden circulatory collapse. None of them was premature, and the indications for antibiotic treatment were either concerned with the labour (premature rupture of the membranes etc.) or such subsequent conditions as "respiratory distress" and "lethargy". No pathogenic organisms were found in any material examined (blood, urine, nasopharynx) either before or after treatment, or at post mortem. Some information is given about previous use of antibiotics generally in this unit, which has evidently been subject to various trends, the popularity of chloramphenicol dating only from 1957. No definite future policy is adumbrated, except the maintenance of "a high level of suspicion" that illness may be the result of treatment rather than of any previous disease.

L. P. Garrod

RYAN, W. L., WILLIAMS, P. T. & IGEL, H. J. **A Disposable Tube Dilution Test.** *Antibiotics & Chemotherapy.* New York. 1961, May, v. 11, No. 5, 307–11, 2 figs.

This device is a circular plastic box on the wall of which are tubes containing a shelf on which a measured amount of antibiotic solution has been dried. The central space contains broth. In use this is inoculated, and can then be allowed to flow into all the tubes from below in a volume of 1 ml. each. After re-closure inversion is carried out to immerse and dissolve the antibiotics, and incubation follows. The medium is thioglycollate broth containing phenol red: a colour change will thus indicate growth and hence resistance to the antibiotic. 2 tubes containing different amounts are recommended for each antibiotic, inhibition by both indicating full sensitivity. Its use in 300 cases in general practice has been found a good guide to the outcome of treatment.

[Since this paper has appeared in a widely read journal it must be taken seriously. To anyone acquainted with the pitfalls of this type of work it seems astonishing that anyone should be satisfied with such a method or ready to encourage practitioners to rely on it. It is evident, although nowhere actually stated, that the inoculum is material direct from the patient. How often must it be said that any such material except certain "puncture fluids" contains non-pathogenic as well as pathogenic bacteria, and that successful clinical bacteriology depends more on separating them than on anything else? Another objection to such devices is that the simple medium used will not permit the growth of some of the more fastidious pathogens, even in pure culture. To suggest, as the authors do, that this crude and fallacious method is superior to others for "routine studies of synergism" is an all-time high for misguided optimism.]

L. P. Garrod

BRANDL, E., CARILLI, A. & CHAIN, E. B. Terreni colturali semplici per produzione di penicillina. [**Simple Media for Penicillin Production**] *Rendiconti Istituto Superiore di Sanità.* Rome. 1961, v. 34, Pts. 2/3, 205–21. [11 refs.] English summary (7 lines).

BRANDL, E., CARILLI, A. & CHAIN, E. B. Produzione di penicillina con micelio lavato di *Penicillium chrysogenum*, in terreni di sostituzione chimicamente definiti. [**Penicillin Production by Washed Mycelium of *Penicillium chrysogenum* in Replacement Media**] *Rendiconti Istituto Superiore di Sanità.* Rome. 1961, v. 34, Pts. 2/3, 222–33. English summary.

BRINGHURST, M. & MARCUS, S. **Antibacterial Action of Penicillin in combination with Serum Globulins: *in vitro* Evaluation.** *J. Lab. & Clin. Med.* 1961, June, v. 57, No. 6, 874–82. [21 refs.]

These experiments were done with 3 strains of pathogenic staphylococci possessing different degrees of resistance to penicillin. In determinations of the minimum inhibitory concentration in broth, this concentration was lower when gamma globulin was added to the medium, the degree of difference depending on the amount added (the largest amount in one test, 10 mgm./ml., reduced the inhibitory concentration of penicillin from 6·3 to 0·09 μgm./ml.). Whole serum had a similar but much lesser effect, and albumin had none. [As the authors point out, albumin binding has been found to reduce the activity of penicillin (this *Bulletin*, 1947, v. 22, 790). They suggest that "with improved methods of purification of penicillin the binding capacity has been reduced", but this explanation of any discrepancy seems most improbable.] The addition of gamma globulin to nutrient agar also increased the width of inhibition zones produced by penicillin discs, whole serum again having a similar effect. The authors suggest that routine tests of sensitivity should be done with such additions, because the tests will then take into account the factor of the body defences. [Unless different strains are affected to different degrees, which does not appear to have been shown, there is no evident advantage in complicating the test in this way, even if these rather unexpected results can be verified.] *L. P. Garrod*

HOEPRICH, P. D. **Side Chain Stereoisomerism and Antistaphylococcal Potency of Penicillins.** *J. Clin. Investigation.* 1961, May, v. 40, No. 5, 783–93, 4 figs. [21 refs.]

This paper from Salt Lake City appears involved, but the actual work reported was simple. The material was 200 strains of "tellurite-positive" [this *Bulletin*, 1960, v. 35, 802] staphylococci from 4 sources, lesions and noses respectively within and outside the hospital; their coagulase reaction is not mentioned, and there is no means of knowing how many of them were normally sensitive to penicillin, but numbers varying from 122 to 134, according to the type of penicillin used in the test, were found to produce penicillinase. It was assumed that they would include strains forming widely varying amounts of the enzyme. The capacity of 6 different penicillins to inhibit their growth was determined at only 3 concentrations: they are given in μmoles, the equivalent of which for benzyl penicillin is 0·37, 3·7 and 37 μgm./ml. and for the others very slightly different values (it seems a little pedantic to insist on this method of measurement and expression in a test employing 10-fold differences). Tubes not showing growth were subcultivated to determine whether the organism had also been killed. On the basis of the percentage of strains inhibited or killed the 6 penicillins are placed in the following order of activity: phenoxymethyl = L-α-phenoxyethyl = DL-α-phenoxyethyl > benzyl > D-α-phenoxyethyl > aminocarboxybutyl. [Whether because of the method used or for some other reason, these findings fail to reveal the greater activity of α-phenoxyethyl penicillin against resistant staphylococci, due to its slower inactivation by penicillinase, which has been consistently found by other workers.] *L. P. Garrod*

LACHOWICZ, T. M. **The Mechanism of Development *in vitro* of Penicillin-Resistant Variants of *Staphylococcus aureus*. I. The Effect of Drug Concentration on the Number of Resistant Forms.** *Acta Microbiologica Polonica.* 1960, v. 9, No. 2, 133–42, 5 figs. [29 refs.] **II. Further Investigation on the Fluctuation Test in the Study of Origin of Penicillin-Resistance.** *Ibid.*, 143–50, 1 fig. [11 refs.]

These papers are part of a doctoral thesis for the University of Wroclaw and are difficult to follow, owing in part to imperfect translation.

I. Among the miscellaneous experiments described was a study of "rest cell divisions" in staphylococcus 209 growing on critical concentrations of penicillin, which involved enumerating the cocci in micro-colonies at different stages of incubation. Visible colonies were also counted and measured on 8 different concentrations of penicillin between 0·01 and 0·08 unit per ml. after 1, 2 and 3 days' incubation, and the behaviour of subcultures from them was examined. The main conclusion reached is that 1-step mutants are heterogeneous in their degree of penicillin resistance; reference is also made to "physiological differences".

II. The fluctuation test was applied to the study of penicillin resistance in staphylococcus 209. Suspensions of 25 single colonies and of a mixture of 10 were plated on media containing 0·045, 0·05 and 0·07 unit per ml. The variation in the number of colonies obtained was much greater from single cells than from the mixture. 4 distinct colonial types obtained each exhibited a constant pattern of penicillin resistance (*i.e.*, in the proportion of cells growing on different concentrations). This is held to support the clonal origin of resistant organisms and thus the mutational theory of resistance.

L. P. Garrod

DINEEN, P. **The *in vivo* Production of Penicillinase by Hemolytic *Staphylococcus aureus*.** *J. Immunology.* 1961, May, v. 86, No. 5, 496–504, 9 figs. [21 refs.]

According to this author, penicillinase production *in vivo* has never been demonstrated. After various fruitless attempts he has succeeded in doing this. Mice were inoculated intravenously with staphylococcus culture: 7 strains were used, 5 being resistant and 2 sensitive to penicillin. After 5 days the kidneys, which are the principal site of infection, were removed and rapidly homogenized, the suspension so produced being then sterilized by shaking with chloroform. Some of this was then placed in a well in a plate of nutrient agar containing *Sarcina lutea* and different concentrations of penicillin. The *Sarcina* grew round the wells containing kidney homogenate from mice infected with resistant strains but not sensitive ones. This growth occurred

when the medium contained 0·02 or 0·03 but not 0·05 unit per ml. of penicillin. There was no penicillinase activity in kidneys removed immediately after inoculation of the mouse: therefore the activity found had been produced during the course of the infection.

L. P. Garrod

THOMAS, R. **Colorimetric Detection of Penicillins and Cephalosporins on Paper.** *Nature.* 1961, Sept. 16, v. 191, 1161–3, 2 figs.

URI, J. & SZTARICSKAI, F. **Simple, Quick Methods for Detection of 6-Amino-Penicillanic Acid.** [Correspondence.] *Nature.* 1961, Sept. 16, v. 191, 1223, 1 fig.

PROC. ROY. SOC. Ser. B. 1961, Aug. 15, v. 154, No. 957, 478–531, 9 figs. [Numerous refs.] **6-Aminopenicillanic Acid.**

These 6 papers by members of the staff of Beecham Research Laboratories describe some of the work which made it possible to produce 6-aminopenicillanic acid (6-APA) in quantity and thus led to the discovery of the newer "synthetic" penicillins. Although various production methods are described, the papers do not refer to any of them as actually used in manufacture.

(1) F. R. BATCHELOR, E. B. CHAIN and G. N. ROLINSON, *6-aminopenicillanic acid in penicillin fermentations,* (pp. 478–489).

The fact that 6-APA is formed at all by *Penicillium chrysogenum* was first detected by a discrepancy between the results of assays by two different methods of penicillin fermentation. These were a biological method which estimated penicillin only and a chemical method which detected both substances. It was then found that if the precursor, *p*-aminophenylacetic acid, was omitted from the fermentation medium, the yield of 6-APA was much higher. The rest of the paper is concerned with conditions governing the yield of 6-APA, including composition of the medium and with special reference to the degree of aeration.

(2) M. COLE and G. N. ROLINSON, *Formation of 6-aminopenicillanic acid by Emericellopsis minima (Stolk) and related fungi,* (pp. 490–497).

This fungus, like certain *Cephalosporium* spp., forms cephalosporin N, which is a penicillin. It was therefore of interest to determine whether it forms 6-APA. Confirmation was obtained that it does, together with cephalosporin N and 2 other unidentified antibiotics. It also forms penicillin amidase, the enzyme which separates 6-APA from its side chain. This amidase acted rapidly on phenoxymethyl penicillin, much less on benzyl penicillin and not at all on cephalosporin N. Some other fungi related to *E. minima* were examined with similar results.

(3) F. R. BATCHELOR, E. B. CHAIN, T. L. HARDY, K. R. L. MANSFORD and G. N. ROLINSON, *Isolation and purification,* (pp. 498–508).

This is a purely technical paper describing methods for extracting and purifying 6-APA, giving details of culture medium, assay methods and percentage yields at different stages.

(4) G. N. ROLINSON and SHIRLEY STEVENS, *Antibacterial activity,* (pp. 509–513).

6-APA has a low degree of activity against Gram-positive organisms (*Corynebacterium* spp. excepted), but an activity more nearly approximating to that of benzyl penicillin against many Gram-negative bacilli. This general rule is illustrated by determinations of the minimum inhibitory concentrations of both for 27 species, including multiple strains of some. 6-APA is bactericidal in concentrations very little higher than the bacteriostatic. It causes morphological changes like those produced by benzyl penicillin, suggesting a similar action on the bacterial cell wall. Staphylococci trained to resist 6-APA become resistant to benzyl penicillin and *vice versa.*

(5) F. R. BATCHELOR, J. CAMERON-WOOD, E. B. CHAIN and G. N. ROLINSON, *6-aminopenicillanic acid as a substrate for penicillinase and an inducer of penicillinase formation,* (pp. 514–521).

This paper compares the actions of *Staphylococcus* and *Bacillus cereus* penicillinases on 6-APA and on benzyl penicillin, which have distinct *p*H optima and also exhibit other differences. It was also shown that 6-APA acts like benzyl penicillin as an inducer of penicillinase formation in staphylococci.

(6) F. R. BATCHELOR, E. B. CHAIN, M. RICHARDS and G. N. ROLINSON, *Formation of 6-aminopenicillanic acid from penicillin by enzymic hydrolysis,* (pp. 522–531).

A penicillin amidase which can be used to prepare 6-APA from penicillin is formed by numerous organisms of 2 kinds. Some bacteria form an amidase which acts most readily on benzyl penicillin (a further paper is promised on this). An amidase acting much more readily on phenoxymethyl than on benzyl penicillin is formed by some moulds and other fungi: 215 species were examined, with positive results in 38. That chosen for further study was the amidase formed by a strain of *Streptomyces lavendulae.* The rest of the paper describes a study of the conditions governing the formation of 6-APA from phenoxymethyl penicillin by this enzyme.

L. P. Garrod

ROLINSON, G. N. & STEVENS, Shirley. **Microbiological Studies on a New Broad-Spectrum Penicillin, "Penbritin".** *Brit. Med. J.* 1961, July 22, 191–6, 5 figs.

This and the 3 succeeding papers [see below] are about a new "synthetic" penicillin, *i.e.* one prepared synthetically from naturally formed 6-aminopenicillanic acid, by workers at Beecham Research Laboratories. This substance is 6[D(−)α-aminophenylacetamido] penicillanic acid (trade name Penbritin). It is acid-stable and can therefore be administered orally.

Its most important property is the wide range of its antibacterial activity. These authors report minimum inhibitory concentrations for multiple strains of many species, comparison being made with penicillin G, tetracycline and chloramphenicol. Penbritin has a similar activity to that of penicillin G against streptococci,

staphylococci and pneumococci, and a greater one than that of G, comparing favourably with those of tetracycline and chloramphenicol (in some instances indeed slightly exceeding these), against *Escherichia coli* and *Salmonella, Shigella* and *Proteus* spp. *Pseudomonas pyocyanea* and *Klebsiella aerogenes* (but not *Klebsiella pneumoniae*) are resistant. Penbritin is destroyed by staphylococcal penicillinase, and there is evidence of its destruction by the corresponding enzymes formed by certain coliforms. Inoculum size and the presence of serum affect its activity very little: *p*H has little effect on its action on staphylococci, but an acid reaction increases its activity against *E. coli* and *Streptococcus faecalis*. It is bactericidal in concentrations little in excess of the inhibitory at a rate similar to that of penicillin G. Organisms can become much more resistant to it by gradual stages when grown in increasing concentrations. *L. P. Garrod*

Brown, D. M. & Acred, P. **"Penbritin"—a New Broad-Spectrum Antibiotic. Preliminary Pharmacology and Chemotherapy.** *Brit. Med. J.* 1961, July 22, 197–8, 1 chart.

This paper reports very briefly the favourable results of toxicity tests with Penbritin, and of therapeutic tests against 4 infections in mice, in which the CD50 was found to be lower (in some instances much lower) than that of tetracycline or chloramphenicol. Administration of 20 mgm. per kgm. orally to dogs followed by serial blood assays showed a peak higher and later than those produced by the same dose of penicillin V or phenethicillin, and a slower fall with longer persistence.
L. P. Garrod

Knudsen, E. T., Rolinson, G. N. & Stevens, Shirley. **Absorption and Excretion of "Penbritin".** *Brit. Med. J.* 1961, July 22, 198–200, 2 figs.

Single capsules of Penbritin containing 250, 500, 750 or 1000 mgm. were given to groups of normal subjects, and the drug concentration in the blood was determined after ½, 1, 2, 4 and 6 hours. The peak concentration was reached at 2 hours and the means found at that time after the 4 doses named were 1·94, 3·8, 5·1 and 6·79 μgm. per ml.: these levels are in direct proportion to the dose [whereas with some other antibiotics given orally, notably tetracyclines, the larger the dose the less is the proportion of it absorbed, at least as indicated in this way]. Substantial levels were still found at 4 hours, and low levels, but detectable in every subject even after the smallest dose, at 6 hours. Excretion in the urine during this period varied from 25 to 33% of the dose: measured over 24 hours after a 500 mgm. dose it was from 22 to 41%. When 500 mgm. were given at 8-hour intervals for 4 days there was no accumulation in the blood. It is concluded that doses of 250–750 mgm. at 6- or 8-hour intervals, according to the nature of the infection, should be therapeutically suitable.
L. P. Garrod

Stewart, G. T., Coles, H. M. T., Nixon, H. H. & Holt, R. J. **"Penbritin": an Oral Penicillin with Broad-Spectrum Activity.** *Brit. Med. J.* 1961, July 22, 200–206, 3 figs. [13 refs.]

This paper reports some preliminary clinical trials with Penbritin, together with some studies of its *in vitro* and pharmacological behaviour, whose results correspond with those in the preceding papers.

The antibiotic was given orally in doses of 50–100 mgm. per kgm. daily to 28 patients—all children. In 8 with urinary tract infections due to organisms of demonstrated sensitivity the urine was invariably rendered sterile in 2–4 days, although relapse or re-infection occurred later in 2 predisposed patients, and 1 developed a group D streptococcus meningitis during treatment. High concentrations (up to 4000 μgm. per ml.) were found in the urine.

The attempted treatment of intestinal carriers was much less successful: it failed in each of 6 patients with *Salmonella typhimurium* (although 1 was cleared up after a second course) and in 2 of 3 with pathogenic *Escherichia coli*: 1 with *Shigella sonnei* was cleared. [The duration of these carrier states, and indeed of the courses of treatment given, is not stated.]

Among other miscellaneous cases, a good and rapid response was obtained in peritonitis due to *Salm. typhimurium*, and the streptococcal meningitis already mentioned responded to intraventricular injection of Penbritin. No ill effects were seen except rashes in 3 patients: 1 known to be sensitive to penicillin G was shown also to be sensitive to Penbritin. *L. P. Garrod*

Watters, J. L. & Gaulden, E. C. **Semisynthetic Penicillins. Observations based on Preliminary Reports.** *Current Therap. Res.* New York. 1961, Aug., v. 3, No. 8, 333–44, 4 graphs. [18 refs.]

This paper reports a comparison between the D- and L-isomers of α-phenoxyethylpenicillin (phenethicillin). Their minimum inhibitory concentrations for *Streptococcus pyogenes, Staphylococcus aureus* and *Strep. pneumoniae* were determined in multiple tests with both single strains and 10 different ones of each, and the L-isomer was the more active against each species, the degree of difference increasing in the order named. Single oral doses of each were given to numerous volunteers and the blood level determined after ½, 1, 2, 4 and 6 hours both by a plate assay for the w/v concentration and by a dilution test with organisms of the same 3 species. The results of the w/v assays are not given, although it is stated that the L-isomer is the better absorbed. Those of the dilution tests are presented in terms of "area under the curve", and the L-/D- activity ratios so indicated after a 250 mgm. dose are for *Strep. pyogenes* 2·0, *Staph. aureus* (2 strains) 3·2 each, and *Strep. pneumoniae* 6·9. The differences are even greater after a 500 mgm. dose. There is some discussion of other work on the newer penicillins, and the authors' summary embodies conclusions based on such work and not on any described in this paper (*e.g.*, that against some Gram-negative organisms the relative activities of the 2 isomers demonstrated here are reversed).
L. P. Garrod

Douthwaite, A. H., Trafford, J. A. P., McGill, D. A. F. & Evans, I. E. **Methicillin.** *Brit. Med. J.* 1961, July 1, 6–8, 1 chart.

These authors from Guy's Hospital have continued their previous [this *Bulletin*, 1961, v. 36, 173] studies of the clinical use of methicillin. 46 patients with penicillin-resistant staphylococcal infections have been treated, most evidently of a serious nature, including 9 of pneumonia, 4 of septicaemia, 2 of osteomyelitis and 4 of endocarditis. " No case has failed to respond ", but in 6 recrudescences occurred after cessation of treatment. Re-treatment was successful in 4 of these, the others being a fatal endocarditis, and a case of multiple boils the further history of which is not given. The dose used varied from 1 gm. 4 times a day to 750 mgm. 3 times: it was found possible to give lower doses with 0·5 gm. probenecid 4 times a day. A graph representing the means of blood levels in 12 patients given this combination and in 18 given methicillin alone shows a peak nearly twice as high and therapeutic levels for nearly 8 instead of 4 hours from the combination. No acquired resistance was seen in any patient's staphylococcus. A *Staphylococcus albus* endocarditis responded to treatment despite theoretically inadequate blood levels, the inhibitory concentration for the organism being 6·5 μgm./ml. Methicillin was found in the cerebrospinal fluid of a case of meningitis (2·8 μgm./ml.). Some evidence was obtained that sensitization to benzyl penicillin may not always involve sensitivity to methicillin. *L. P. Garrod*

Acred, P., Brown, D. M., Turner, D. H. & Wright, D. **Pharmacology of Methicillin.** *Brit. J. Pharmacol. & Chemotherapy.* 1961, Aug., v. 17, No. 1, 70–81, 4 figs.

Luton, E. F. **Methicillin Tolerance after Anaphylactoid Reactions to Penicillin G.** *J. Amer. Med. Ass.* 1961, July 15, v. 177, No. 2, 152–3.

This paper is concerned with 3 patients, all males, aged 30, 31 and 31, who gave a history of reactions to penicillin, consisting in 1 case simply of urticaria, in 1 urticaria, light-headedness and difficulty in breathing, and in 1 shock, erythema going on to urticaria, nausea and vomiting [the term " shock " is used only in describing this case, and the term " anaphylactoid " seems less applicable to the others, particularly the first-named].

All 3 reacted with a weal to the intradermal injection of 0·01 ml. of a 1000 units per ml. solution of penicillin G, but failed to react to similar tests with methicillin, and tolerated a full therapeutic dose (1 gm.) without ill effects. [This is contrary to the experience of some other workers. Evidently a patient sensitized to penicillin G may or may not be sensitive to methicillin.]

L. P. Garrod

Pakuła, R. & Hulanicka-Bankowska, E. **Streptomycin and Dihydrostreptomycin Resistance Marker of Two Transformable Strains of Streptococci.** *Bull. Acad. Polonaise des Sci.* Warsaw. Sér. Sci. Biol. 1961, v. 9, No. ?, 79–85, 1 fig.

Streptomycin (SM) and dihydrostreptomycin (DSM) might reasonably be expected to behave alike in any biological reaction: this paper records a surprising observation which shows that they do not. Two strains of streptococci, one of Group H and the other less clearly identified, both known to be transformable, were each rendered resistant to SM and DSM separately. DNA from these was used to transform the sensitive cultures, and these transformed cultures were cultivated on medium containing each antibiotic. One strain transformed to resistance to either grew on both. The other, transformed to SM resistance, grew on both, but when transformed to DSM resistance grew freely on DSM medium but produced only about 0·2% of the expected number of colonies on SM. Reciprocal transformation reactions were done with all 4 of these transformed cultures: resistance to both SM and DSM resulted in 3 of these tests, but DNA from the abnormally behaving culture again conveyed resistance to DSM only. The existence of 2 markers of resistance, one normal and one defective, is assumed to explain this result.

L. P. Garrod

Woof, J. B. & Hinshelwood, C. **Chloramphenicol Resistance of *Bact. lactis aerogenes (Aerobacter aerogenes).* I. Adaptive and Lethal Processes in Liquid Media and on Agar Plates.** *Proc. Roy. Soc.* Ser. B. 1961, Jan. 3, v. 153, No. 952, 321–8, 6 figs.

Dean, A. C. R. **II. Production of Highly Resistant Strains in Non-Selective Conditions.** *Ibid.*, 329–38, 2 figs.

1. This paper describes observations of 3 kinds on the action of chloramphenicol on *Bacterium lactis* (*Klebsiella*) *aerogenes*. These were the determination of the effect of drug concentration on the length of the lag period for the untrained organism and for cultures trained to growth in different concentrations, of the time of development of colonies of both trained and untrained organisms on agar containing different concentrations, and of the death rate in different concentrations in a liquid medium lacking a nitrogenous source. Analysis of the findings supports the hypothesis that the phenomena of growth in the presence of the drug are the combined effects of lethal action on some cells and adaptation in the remainder, and not the result of the presence of pre-existent mutants.

2. Observations of another kind suggest that the development of resistance to chloramphenicol in *Klebsiella aerogenes* is the result of adaptation and not of mutation. The evidence is essentially this: that under certain conditions of training, all or almost all the cells of an inoculum grow on a higher concentration than before, and not a " specially endowed " small minority. An inoculum containing 50–100 viable cells was plated both on normal medium and on medium containing 5 μgm. per ml. chloramphenicol. A colony from the latter provided the inoculum for the next drug concentration in a series of 8 rising to 60 μgm. per ml.

Throughout the process the colony count on the drug-containing plate was at least 50% and often 90 or 100% of that on normal medium, showing that the majority of the cells had undergone whatever change was responsible for increased resistance. When the process was continued to higher concentrations (maximum 1000μgm. per ml.) the proportion of viable cells forming colonies sometimes fell, but rose again after intermediate culture in drug-free liquid medium, which is again, as the author says, "quite the reverse of what would be expected from any kind of selective mechanism". *L. P. Garrod*

McCarthy, B. J. & Hinshelwood, C. **Colony Formation by *Bact. lactis aerogenes (Aerobacter aerogenes)* on D-Arabinose Plates.** *Proc. Roy. Soc.* Ser. B. 1961, Jan. 3, v. 153, No. 952, 339–46, 6 figs.

This paper adduces evidence for contesting the belief that the few colonies of *Klebsiella aerogenes* appearing early on a medium in which D-arabinose has been substituted for glucose as sole carbon source are mutants. This evidence was obtained by determining the numbers of colonies reaching certain sizes in different times from inocula of different magnitudes from about 10^2 to 10^8. This shows a wide distribution of rates of adaptation, sufficiently explaining the early growth of a few cells in a heavy inoculum without assuming mutation.

L. P. Garrod

Van der Hem, G. K., Meyler, L., Israels, A. A., Sluiter, H. J. & Nieweg, H. O. Bloedafwijkingen door het gebruik van chlooramfenicol. [**Blood Disorders due to Chloramphenicol**] *Nederl. Tijdschr. v. Geneesk.* 1961, Aug. 19, v. 105, No. 33, 1629–34, 2 figs. [14 refs.]

The English summary appended to the paper is as follows:—

"Four cases of pathologic changes of the blood caused by chloramphenicol medication are presented. Three patients died; in two of these cases bone marrow failure was the cause of death.

"An enquiry among practising Dutch internists and paediatricians and data obtained from the Central Bureau of Statistics revealed at least 24 cases of blood dyscrasia following chloramphenicol medication in 1959. Fifteen of these 24 patients died.

"The great value of chloramphenicol as an antibiotic has been established beyond doubt, but on account of its possible side effects it should only be given in diseases for which this drug is strictly indicated. Prophylactic administration is definitely contra-indicated, as well as its use in fever of unknown etiology and in all minor infections or inflammations in which other, less dangerous, antibiotics would be effective."

Phadke, M. V., Joshi, V. S. & Naik, S. G. **Toxicity of Chloramphenicol in Children.** *J. Indian Med. Ass.* 1961, July 1, v. 37, No. 1, 26–30. [17 refs.]

"4 cases of toxicity due to chloramphenicol administered for enteric fever are described.

"Literature on chloramphenicol toxicity is reviewed.

"Blood transfusion and steroids with other supportive treatment seem to hasten recovery in such cases, since all these cases were discharged with gratifying results."

Kohn, K. W. **Mediation of Divalent Metal Ions in the Binding of Tetracycline to Macromolecules.** *Nature.* 1961, Sept. 16, v. 191, 1156–8, 4 figs. [14 refs.]

Roberts, C. E., Jr., Perry, D. M., Kuharic, H. A. & Kirby, W. M. M. **Demethylchlortetracycline and Tetracycline. A Critical Comparison: *in vitro* Activity, Serum Concentrations, and Effect of Serum Binding.** *Arch. Intern. Med.* 1961, Feb., v. 107, No. 2, 204–11, 4 figs. [16 refs.]

Single doses of 0·3 gm. demethylchlortetracycline (DMCT) or 0·5 gm. tetracycline (T) were given to normal subjects, and the antibiotic was assayed in the blood after 2, 4, 6, 12 and 24 hours by inoculating 2-fold dilutions of the serum in broth with dilute culture of a Group A streptococcus also containing blood. In terms of activity against this streptococcus, the levels attained by DMCT were lower than those attained by T, but since the streptococcus was twice as sensitive to the former, the absolute levels of DMCT were relatively much lower (about one-third of those attained by T).

The effects of repeated doses were also studied: detailed findings are given only for days 1 and 5 in a 4-day course of treatment and show almost negligible levels of DMCT, compared with high levels of T, on day 1, and approximately equal levels on day 5.

In many of the assays, growth occurred in the 1 in 2 dilution of serum but not in several subsequent ones: this is attributed to inactivation of the antibiotic by serum binding, and it was shown in separate experiments that 50% serum reduces the activity of DMCT 20-fold and that of T 9-fold. The minimum inhibitory concentrations of the 2 antibiotics for 50 strains each of Group A streptococci, staphylococci and "coli-aerogenes" and 25 of pneumococci were determined: a majority were twice as sensitive to DMCT as to T, and in a few the differences were greater.

The authors conclude by questioning whether the smaller dose of DMCT usually employed can be as effective as the regular dose of T, and suggest that should the dose of DMCT be raised, gastro-intestinal side effects may give trouble.

[The findings in this paper on blood levels are irreconcilable with those of others who have carried out similar studies. This applies both to the peak level and to persistence: it is indisputable that the DMCT level falls more slowly, but in Fig. 1, showing the effects of single doses, DMCT falls to *nil* at 24 hours and T is still fairly high. This is the precise opposite of what should have been found. The results are given only as mean values in 15 subjects, without any individual figures.]

L. P. Garrod

HAMNER, M. E. **Compatibility of Zinc Cation with Demethylchlortetracycline Hydrochloride.** *Antibiotics & Chemotherapy.* New York. 1961, Aug., v. 11, No. 8, 498–500, 1 fig.

KOOIJ, R. **Allergic Contact Dermatitis due to Neomycin. Cross-Sensitivity with other Antibiotics; and Positive Patch Tests with the Isomeric Compounds Neomycin B and Neomycin C and with Neamine.** *South African Med. J.* 1961, May 20, v. 35, No. 20, 406–11, 2 figs. [14 refs.]

This paper reviews the literature on sensitization to neomycin [see, for example, this *Bulletin*, 1960, v. 35, 493], and reports a study of 7 such patients, on whom patch tests were done, with 3% or even 6% neomycin in paraffinum molle: these high concentrations were found to elicit reactions when lower ones did not. All 7 patients reacted to these preparations, as did 5 of them when tested with 6% neomycin B, neomycin C and neamine (4 patients). Similar tests were done with other antibiotics: 5/6 patients reacted with framycetin (which is not surprising since this is a very closely related antibiotic), 3/7 to chloramphenicol, 3/7 to tetracycline, 2/7 to chlortetracycline, 2/5 to bacitracin, but none to streptomycin. An 8th patient, sensitive to streptomycin, did not react to neomycin or any other of these antibiotics. On this basis the author questions the doctrine that neomycin can safely be used as a local application because it will not interfere with the subsequent parenteral use of other antibiotics. [This evidence of cross-sensitization, obtained only by using exceptionally concentrated preparations, seems to require confirmation by other means before this warning need be heeded. It is not mentioned that any patient reacting to, *e.g.*, 6% chloramphenicol or tetracycline was given this drug to verify that treatment with it would have any untoward effects.] Details are given of each patient tested.

L. P. Garrod

i. MCGUIRE, J. M., BONIECE, W. S., HIGGENS, C. E., HOEHN, M. M., STARK, W. M., WESTHEAD, J. & WOLFE, R. N. **Tylosin, a New Antibiotic: I. Microbiological Studies.** *Antibiotics & Chemotherapy.* New York. 1961, May, v. 11, No. 5, 320–27.

ii. HAMILL, R. L., HANEY, M. E., Jr., STAMPER, Martha & WILEY, P. F. **II. Isolation, Properties, and Preparation of Desmycosin, a Microbiologically Active Degradation Product.** *Ibid.*, 328–34, 1 fig. [11 refs.]

These are further papers (several have already appeared) on a new antibiotic isolated in the Lilly Research Laboratories. It is formed by 2 strains of what is believed to be *Streptomyces fradiae* (the source of neomycin) obtained from soil collected in Thailand.

i. This paper briefly describes production methods and gives details of *in vitro* and *in vivo* activity. Tylosin is highly active against Gram-positive cocci, *Corynebacterium diphtheriae*, pleuropneumonia-like organisms and 2 mycobacteria (no data for *Mycobacterium tuberculosis*) and much less active against most Gram-negative species: no action was demonstrable against 4 fungi. Concentrations only slightly above the inhibitory are bactericidal. Resistance increases substantially during 10 transfers on antibiotic-containing medium, and there is some cross-resistance with erythromycin but none with penicillin. Some of these experiments were also done with desmycosin, a substance obtainable by acid treatment of tylosin as described in paper 2: this has similar activity, and both are much more active at *p*H 8·0 than 6·0. Tylosin has a low toxicity, and protects mice against infection with streptococci, staphylococci, pneumococci and *Haemophilus influenzae* when administered either subcutaneously or orally: large doses subcutaneously (but not orally) are also protective in experimental tuberculosis. Among virus infections, meningopneumonitis was susceptible and murine encephalomyelitis and influenza were not.

ii. This paper describes in detail the processes employed for extracting and purifying tylosin, its chemical and physical properties, and the preparation from it of salts, esters, and desmycosin, the antibiotically active derivative referred to in paper i. These antibiotics belong to the group of macrolides. Whether they have any properties superior to those of other macrolides (*e.g.*, erythromycin) is not clear. *L. P. Garrod*

MASON, D. J.; DIETZ, A.; SMITH, R. M.; HANKA, L. J.; SOKOLSKI, W. T.; LEWIS, C.; CLAPP, H. W. **Actinospectacin, a New Antibiotic. I. Discovery and Biological Properties** [MASON, DIETZ & SMITH]. *Antibiotics & Chemotherapy.* New York. 1961, Feb., v. 11, No. 2, 118-22, 1 fig. **II. Microbiological Assay** [HANKA, MASON & SOKOLSKI]. *Ibid.*, 123–6, 3 figs. **III. *In vitro* and *in vivo* Evaluation** [LEWIS & CLAPP]. *Ibid.*, 127–33.

These papers are from the Research Laboratories of the Upjohn Co.

I. Actinospectacin is formed by *Streptomyces spectabilis*. The paper describes this organism, defines the medium used for production, but not the method of extraction, and states the minimum inhibitory concentrations of actinospectacin for 14 species of bacteria. These range from a minimum of 4 to a maximum of 500 (mostly 16–64) μgm./ml. It has no action on 14 pathogenic fungi, 3 protozoa or 1 sarcoma.

II. A purely technical paper on assay methods. *Klebsiella pneumoniae*, the most sensitive organism, is used for these. One method for detecting the organism in the blood involves the addition of a sub-inhibitory concentration of streptomycin in order to render low concentrations detectable.

III. This gives more extensive information on *in vitro* activity, comparison being made with chloramphenicol, and the minimum inhibitory concentrations found are generally lower than those given in paper I. Both Gram-positive and Gram-negative species are sensitive. Concentrations 4–10 times greater than the bacteriostatic are bactericidal: serum does not interfere. Resistance appears rapidly in staphylococci, and to a lesser extent in other species. *In vivo* performance is said to be better than *in vitro*, and brief particulars are given of the results of therapeutic tests against many infections, mainly in mice, comparison again being made with

chloramphenicol. The subcutaneous was much more effective than the oral route of administration.

[There are some unusual omissions from these papers —*e.g.*, no accounts of physical or chemical properties of the antibiotic, of studies of absorption and excretion, or of toxicity tests—and it is not clear whether the authors think it may have a therapeutic future or are merely placing their work on record as a matter of academic interest, unless the fact that it has been given a trade name (Trobicin) points to the former conclusion.]

L. P. Garrod

McCarthy, C. G. & Finland, M. **Furaltadone. Antibacterial Activity *in vitro* and in Serum of Patients during Treatment.** *Arch. Intern. Med.* 1961, June, v. 107, No. 6, 863–71. [19 refs.]

This paper is an uncompromising condemnation of furaltadone, the nitrofuran compound intended for the systemic treatment of certain bacterial infections, particularly staphylococcal. Studies of *in vitro* activity generally confirmed the results of other workers [this *Bulletin*, 1961, v. 36, 480] but it is pointed out that when the size of the inoculum is increased, the concentration required to inhibit growth also increases to unpromising levels. The drug was given intravenously to 9 patients, whose case histories are given: the majority of these were suffering from staphylococcal infections, sometimes complicated by others due to more resistant bacteria. By reason of age or other underlying diseases or both they appear to have been very unfavourable cases, but the lack of any benefit from the treatment is not so much relied on as the failure to detect the drug in the blood by a biological method.

Previous authors [*loc. cit.*] have demonstrated levels theoretically capable of antibacterial action in some specimens by a chemical method: these authors used a test involving inhibition of growth of a small inoculum of a sensitive staphylococcus, and apparently failed to detect any activity except that afforded by residues of previously or simultaneously administered antibiotics [this is the verdict on the results in the discussion, although it is not clear from the accounts of all cases that positive findings could be so explained]. Low concentrations were found in urine and none in bile from 2 patients. No drug was detectable in any specimen of blood from 12 patients given furaltadone alone prophylactically as post-operative cover, and 2 of these patients developed serious infections during the treatment, a staphylococcal pneumonia and bacteriaemia, and a lung infection caused by pneumococci and *Haemophilus influenzae*. (These 12 patients were among a series of 50 reported on unfavourably by Byrne and Goldsmith. *New England J. of Med.*, 1960, v. 263, 962.)

L. P. Garrod

Metzger, W. I. & Jenkins, C. J., Jr. **Relative Antimicrobial Activity of Topical Chemotherapeutic Compounds when tested, *in vitro*, in the Presence and Absence of Human Serum.** *Antibiotics & Chemotherapy.* New York. 1961, May, v. 11, No. 5, 335–9. [18 refs.]

These authors first point out that synthetic antibacterials have 2 advantages over antibiotics for treating skin infections: they do not (often) sensitize nor do bacteria acquire resistance to them. Their paper is in praise of dequalinium chloride as an agent with promising anti-bacterial activity for this purpose: this is more fully described as "a salt of decamethylenebis[4-aminoquinaldinium chloride]". In these tests it was compared with 4 quaternary ammonium compounds, hexachlorophene, bithionol, thimerosal and a flavine derivative, phenacridane chloride: 2-fold dilutions of all these in broth were inoculated with *Streptococcus pyogenes*, *Staphylococcus aureus*, an apparently unidentified *Klebsiella* and *Candida albicans*, to determine the lowest concentration inhibiting growth. A parallel set of tests was done in broth with 20% serum. Dequalinium chloride inhibited 3 of these organisms in concentrations of 1·56–6·25μgm./ml.: the *Klebsiella* was much more resistant to this and to almost all the other compounds (it would perhaps have been more informative to have tested a well identified strain of, say, *Escherichia coli*). Some of the other compounds were a little more active against some species in broth, but dequalinium chloride was alone in the lack of any impairment of its activity by serum. That of all the others was reduced by serum, often 8-fold and sometimes much more.

L. P. Garrod

Stur, D. Eine Methode zur quantitativen Bestimmung der Bakterizidie chemischer Desinfektionsmittel. **[A Method for the Quantitative Estimation of the Bactericidal Action of Chemical Disinfectants]** *Zent. f. Bakt.* I. Abt. Orig. 1961, v. 182, No. 2, 251–60, 4 figs. [12 refs.]

This author from Vienna begins with the usual and well-justified criticism of "end-point" methods of measuring bactericidal action, and proposes the substitution of a series of viable counts on the test mixture. This is sampled wth a calibrated dropping pipette, the aliquot removed being diluted, if necessary in a solution containing a neutralizer, and survivors in this and further dilutions are enumerated by the method of the surface viable count. Two graphs showing the progress of bactericidal action as determined in this way are reproduced, one showing the action of different concentrations of formalin, the other a composite graph showing the dependence on concentration with and without 20% of serum, of the action of formalin, benzalkonium chloride, phenol, a cresol soap solution and a chlorinated benzylphenol. It is pointed out that various coefficients can be calculated from such data: the preferred method of expressing the result is as the time required to achieve a 99·999% mortality. The paper is concerned chiefly with principles and theory: not enough technical detail is given to furnish the basis of a standard method.

L. P. Garrod

Lammers, T. & Tuncer, O. Zur tuberkuloziden Wirkung des gasförmigen Aethylenoxyds. **[The Tuberculocidal Action of Gaseous Ethylene Oxide]** *Gesundheitswesen u. Desinfektion.* 1961, Jan., v. 53, No. 1, 1–4. [14 refs.]

Pieces of linen were contaminated with either a culture of tubercle bacilli or with infected sputum (no details of

their preparation are given, but the layer of sputum is later referred to as "thin"), treated in either the wet or dry state with ethylene oxide, and then cultivated or injected into guineapigs. The gas was used as a 15% mixture in CO_2 in 2 ways. At a pressure of 3 atmospheres and a temperature of 45°C., the bacilli were consistently killed in 10 minutes and sometimes in 7½. At atmospheric pressure in a gas-tight plastic bag which would accommodate such objects as pillows and mattresses the time required was 24 hours. The dried bacilli were only slightly more resistant than the moist, and staphylococci in parallel experiments were killed at almost exactly the same rate. *L. P. Garrod*

Bruhin, H., Bühlmann, X., Vischer, W. A. & Lammers, T. Sterilisation mit Äthylenoxyd unter besonderer Berücksichtigung der Anwendung bei Kunststoffen. **[Sterilization with Ethylene Oxide with particular Reference to its Use for Plastics]** *Schweiz. med. Woch.* 1961, May 20 & 27, v. 91, Nos. 20 & 21, 607–13; 635–9, 2 figs. [87 refs.]

This paper is in the main a review of the literature on ethylene oxide, defining its physical properties and the forms, usually admixtures with CO_2 or other substances, in which it is available (with trade names) and methods of assay. The findings of many other workers about its bactericidal action on different bacterial species under different conditions of concentration, temperature and pressure are set forth in 4 tables: a 5th presents similar data for viruses. Toxicity is also discussed at length. A further table reproduces the results of 5 authors who studied the sterilization of various materials sealed in plastic wrappings. The authors' own experiments concern materials not only wrapped in but made of plastic, *viz.*, plastic Petri dishes. Using a specified German apparatus, they found that these dishes, when contaminated with spores or crude soil, could regularly be sterilized in 60 minutes by 1200 mgm per litre ethylene oxide at a pressure of 6 atmospheres and a temperature of 55°C. The same process is feasible if the Petri dishes actually contain medium, and this will thereafter support growth: liquid media can also be sterilized. A humidity of 10–20% if necessary for dry materials, and penetration through a thick layer of dried infected material may be unsatisfactory. *L. P. Garrod*

Caldwell, D., Cox, W. A., D'Arcy, P. F. & Rowe, L. R. **The Antibacterial Activity of New Derivatives of 4-Aminoquinoline and 4-Aminoquinaldine.** *J. Pharmacy & Pharmacol.* London. 1961, Sept., v. 13, No. 9, 554–64, 6 figs. [10 refs.]

Harris, H. F. & Allison, V. D.; Fallon, R. J.; Rowe, T. W. G. & Kusay, R. **Steam Sterilisation.** [Correspondence.] *Lancet.* 1961, Sept. 9, 603–5.

These letters are concerned with three different aspects of sterilization by steam.

Harris and Allison report thermocouple studies on a high-vacuum sterilizer of 60 cu. ft. capacity, using gloves as their test object. The pre-vacuum was to 20 mm. Hg and the sterilizing temperature was 274°F. (134·4°C.) for 5 minutes. They found considerable temperature differentials within the chamber itself and within the packs; they also found that the lowest temperature was not necessarily indicated by a thermometer in the chamber drain. More seriously they found that the packs did not always reach the sterilizing temperature in the normally recommended exposure period of 3 minutes at 274°F. (134°C.).

The authors conclude that high-vacuum sterilizers should not be accepted from the manufacturers until thermocouple studies made *in situ* have proved satisfactory.

The additional point is made that the choice of size for a new sterilizer should depend not on its nominal capacity, based on the internal dimensions of the chamber, but on the usable capacity after allowance has been made for internal fittings.

Fallon discusses the use of nylon film for wrapping instruments to be sterilized by steam. He found that 9 of 11 new bags had, after sterilizing, holes that could be detected by immersion in water. He points out that both cloth and paper are easier to use than nylon and are freely permeable by steam. Paper has been shown to be quite a good bacterial barrier for packs.

Rowe and Kusay discuss the physics of high vacuum sterilization with special reference to the drying of the load. Textiles should emerge as dry as they started, but with solid objects such as instruments and bowls the considerable amount of condensed water tends to be localized by gravity and may not be vapourized at the post-vacuum stage. The time-honoured process of purging by dry air is sometimes effective: the authors considered that it should be possible to wrap solid objects in a substance which is permeable to water as vapour but not as liquid. Nylon cloth proved unsatisfactory because of condensation inside the pack but good results were obtained by packing the bowls in moulded cases of asbestos fibre. Papier mâché about ¼ in. thick would probably also be suitable.

[Although difficulties have been reported, such as those given above, in the use of high-vacuum techniques for steam, there is little doubt that these are mainly problems of engineering technology, which will soon be overcome.] *J. C. Kelsey*

BACTERIA

The order in this section is:—**Cocci; Donovania; Mycobacterium; Corynebacterium; Haemophilus; Pseudomonas; Pfeifferella; Enteric Organisms; Brucella; Pasteurella; Bacillus; Anaerobes; Spirochaetes; Erysipelothrix; Listeria; Others.**

BLAIR, J. E. & WILLIAMS, R. E. O. **Phage Typing of Staphylococci.** *Bull. World Health Organization.* Geneva. 1961, v. 24, No. 6, 771–84, 4 figs. on 4 pls.

Comparison of staphylococcal phage types requires use of standardized typing methods. A detailed account of suitable methods, approved by the Subcommittee on Phage Typing of Staphylococcus of the International Association of Microbiological Societies, is given in this paper.

The use of 21 basic phages selected by the subcommittee is recommended for routine use, 6 additional phages being mainly useful for reference laboratories. The suggestion is made that papers reporting results of staphylococcal phage typing should mention the phages that were used.

Methods are described for the fairly large-scale production of the typing phages, and necessary precautions are given; thus the phage patterns to be expected of the propagating strains of staphylococci are tabulated. Propagation by the soft-agar technique is preferred for most phages.

A further section deals with the important testing of the phage batches produced, and is particularly concerned with the determination of the lytic spectra of the phages on 16 test strains chosen so that phages of similar lytic spectra can be distinguished. The titres to be expected of the phages on these test strains, as compared with the titres found on the propagating strains, are tabulated according to most recent experience. Criteria whereby batches should be rejected when the titres found differ from these expectations are suggested.

The final section describes typing technique, and a reference is made to mechanical applicators of the phage drops. Reading, reporting, and interpretation of results are usefully discussed, the need for adequate epidemiological information to allow intelligent interpretation of results being justly stressed.

This timely paper should adequately fulfill its purpose of allowing workers to follow a standard proved technique of phage typing. *J. W. G. Smith*

PILLET, J., ORTA, B., FOUCAUD, M. & PERRIER, M. Étude sérologique de 559 souches de staphylocoques pathogènes isolées en France. Répartition et fréquence relative des différents types. [**Serological Studies on 559 Strains of Pathogenic Staphylococci isolated in France**] *Ann. Inst. Pasteur.* 1961, June, v. 100, No. 6, 713–24.

559 strains of coagulase-positive staphylococci, isolated in various parts of France, were tested for serological type by the methods described by Pillet and his collaborators [see *e.g.* this *Bulletin*, 1960, v. 35, 1030]. 105 fell into type I, 184 in type I/II/5 and 108 in type 9/12. 56 strains were untypable or spontaneously agglutinable. "Mixed" types were thus extremely common; details of these are presented. There were no noteworthy differences in the types from the different regions of France. No mention is made of any attempted correlation with the typing scheme devised by OEDING [see *ibid.*, 1961, v. 36, 588]. *R. E. O. Williams*

JETTMAR, H. M. & REISENHOFER, Ursula. Einteilungsmöglichkeiten von Staphylococcus-pyogenes-Stämmen durch das verschiedene Verhalten ihrer Lipasen. [**The Possibility of Subdivision of *Staphylococcus pyogenes* Strains by Differences in the Behaviour of their Lipases**] *Arch. f. Hyg. u. Bakt.* 1961, June, v. 145, No. 4, 274–82, 6 figs,

When staphylococci are grown on nutrient agar containing milk or fat, 2 different sorts of lipolytic activity can be recognized. In 1 an area of clearing with a diffuse edge develops during 24–48 hours' incubation. The second type develops more slowly and has a more sharply defined margin. Possible correlations of these differences with virulence are being explored. *R. E. O. Williams*

CANNON, Frances D. & HAWN, C. V. Z. **Rapid Identification of Coagulase-Producing Staphylococci.** *Amer. J. Clin. Path.* 1961. May, v. 35, No. 5, 468–71, 1 fig. [Reprinted from *Tech. Bull. Registry Med. Technol.* 1961, Apr., v. 31, No. 4, 66–9.]

Bovine fibrinogen was used as a substrate in a rapid test for coagulase production by staphylococci. The results were compared with results of the standard tube test. The rapid test is a modification of the slide coagulase test CADNESS-GRAVES *et al.* [this *Bulletin*, 1943, 18, 870].

The strain was emulsified in water, a drop of 0·2% fibrinogen in buffered saline at *p*H 7·2 was added and the slide was agitated for 1–3 minutes. Coagulase-positive strains were precipitated. For the standard tube test 0·125 ml. of an overnight broth culture was added to 0·5 ml. of undiluted oxalated human plasma and final results were read after 24 hours.

There was good correlation between the 2 tests. When slides were agitated for 3 minutes only 3 of 344 tube-positive strains failed to give positive results and there were no false positive reactions. The slide test was reproducible with 4 different preparations of bovine fibrinogen and the 0·2% preparation was stable for 10 days at 4°C. The test was not influenced by the age of the culture. *M. Patricia Jevons*

BERNHEIMER, A. W. & SCHWARTZ, Lois L. **Extracellular Proteins of Staphylococci.** *Proc. Soc. Exper. Biol. & Med.* 1961, Apr., v. 106, No. 4, 776–80, 2 figs. [20 refs.]

Representative potentially pathogenic and non-pathogenic strains of staphylococci were grown in a

modification of the GLADSTONE and VAN HEYNINGEN medium [this *Bulletin*, 1957, v. 32, 900] for 24 hours. The supernatants of the 7 strains examined were dialysed and concentrated, and the non-dialysable material was examined for extracellular proteins by starch electrophoresis.

The products of one of the potentially pathogenic strains of Phage Type 80/81 were submitted to this technique and the known toxins and enzymes were localized by slicing the gel, staining with amido black and either applying the cut surfaces directly to an appropriate substrate or testing eluates. In this way alpha lysin, lipase, deoxyribonuclease, hyaluronidase and staphylokinase were mapped. (Under the conditions of growth, coagulase was not produced.)

The strains varied in the amounts of extracellular material of high molecular weight which they elaborated during growth. The 2 coagulase-negative strains and the strain of intermediate pathogenicity produced larger amounts of ribonuclease acid as detected with orcenol reagent (9·3–11·8% weight) than the 4 coagulase-positive strains (3·8–4·7%). This may indicate more lysis of the non-pathogenic strains but ribonuclease was detected in the potentially pathogenic strains which may have accounted for the difference.

Electrophoretic patterns of the 4 potentially pathogenic strains showed 12–14 distinct bands and were more complex than those of the non-pathogenic strains which showed only 6 or 7 bands. Most of the proteins were not identifiable with the known staphylococcal toxins previously mapped and represented new extracellular substances. *M. Patricia Jevons*

GAUSE, G. F., KOCHETKOVA, G. V. & VLADIMIROVA, G. B. **Biochemical Changes accompanying Impaired Respiration in Staphylococci.** *Nature.* 1961, June 10, v. 190, 978–80, 1 fig.. [16 refs.]

Mutants of *Staphylococcus aureus* strain 209 selected in the presence of 5-fluoro-2-deoxyuridine were investigated, since it has been shown that some fluorinated pyrimidines prepared as tumour-inhibitory compounds exert a selective inhibitory action on staphylococci.

The parent culture was inhibited by 5-fluoro-2-deoxyuridine and this action was reversed by thiamine but not by uracil. A mutant with respiration deficiency was inhibited by 5 fluoro-uracil and this action was reversed by uracil but not by thiamine. These observations suggested that deoxyribonucleic acid thiamine was synthesized by different pathways by the parent strain and the mutant since 5-fluoro-2-deoxyuridine is known to block the formation of thiamine required for deoxyribonucleic acid.

The respiratory-deficient mutant differed from the parent strain in that the respiratory coefficient was decreased by 40–60% and respiration was less sensitive to cyanide. The cytochrome pattern was altered and there were several biochemical differences which suggested disturbances in deoxyribonucleic acid synthesis.

The mutants produced a red-orange intracellular ethanol-extractable pigment. Absorption spectra of pigment extracts from 9 different respiratory deficient mutants showed maximal optical density at 475 $m\mu$ and pointed to a deficiency in flavin metabolism. Estimation of vitamin B12 showed almost 100-fold increase compared with that of the parent strain. Catalase activity was less.

Cell wall analysis of the mutant showed differences when compared with the parent culture. The mutant contained diaminopimelic acid but only small amounts of lysine, this could indicate absence of the enzyme carrying out decarboxylation of diaminopimelic acid to lysine. All 7 anti-tumour agents tested selectively inhibited the growth of the mutant. One of these, mitomycin C, is known to interfere with deoxyribonucleic acid synthesis. *M. Patricia Jevons*

CONTI, C. R., CLUFF, L. E. & SCHEDER, E. Patricia. **Studies on the Pathogenesis of Staphylococcal Infection. IV. The Effect of Bacterial Endotoxin.** *J. Exper. Med.* 1961, May 1, v. 113, No. 5, 845–60, 1 text fig. & 6 figs. on 3 pls. [18 refs.]

When suspensions of *Staphylococcus aureus* were injected into the skin of rabbits in areas previously injected with *Shigella* or *E. coli* endotoxin a haemorrhagic lesion was produced; the dose of staphylococci was less than that needed to produce even minor lesions in unprepared skin. The endotoxin had to be given within 4 hours before the cocci; it could, however, be given intravenously instead of locally. Endotoxin did not enhance the skin reaction to staphylococcus alpha-toxin, but it seemed that the endotoxin enabled the staphylococci to multiply more rapidly and presumably to produce their toxin, which caused the skin necrosis. Interference with phagocytosis is probably the mechanism involved. Acquired tolerance to endotoxin, induced by repeated doses, abolished its potentiating effect. *R. E. O. Williams*

HIGGINBOTHAM, R. D. & BASS, J. A. **Effect of Mucin and Cortisol on Resistance of Mice to Two Different Strains of *S. aureus* and the Possible Importance of Endotoxin in the Infectious Process.** *Texas Reports on Biol. & Med.* 1961, v. 19, No. 2, 283–99, 5 figs. [26 refs.]

One strain of *Staphylococcus aureus* used, Fritchie, was lethal to mice after intraperitoneal injection. The 50% lethal dose was about 16×10^6 viable cells, and death occurred within 24 hours of injection. It was relatively non-pathogenic by the intravenous route. The second strain, 959, was lethal in similar doses after intravenous injection but was considerably less pathogenic by the intraperitoneal route. This strain caused death within 3–10 days of injection. In the experiments reported both strains were given to groups of mice intraperitoneally.

Mucin injected with the staphylococci considerably enhanced the pathogenicity of the Fritchie strain. It also caused some increase in the poor ability of the 959 strain to kill mice after intraperitoneal injection, and such deaths occurred within 24 hours in a manner similar to those caused by Fritchie cells. Adrenalectomy increased susceptibility, whereas 2·5 mgm. of Cortisol

(hydrocortisone acetate) given 18 hours and 2 hours before the staphylococci decreased susceptibility to such acute toxic deaths.

Much of the increased susceptibility to the early toxic effect provoked by giving mucin with the staphylococci could be prevented by prior injection of Cortisol in the doses mentioned above. However, mice which had had Cortisol were increasingly liable to die between 3 and 10 days, this effect being marked when the 959 strain was used. The authors point out that such late decrease in resistance produced by Cortisol could be due to adrenal insufficiency resulting from the large doses of the drug used.

Injection of a commercial staphylococcal endotoxin, apparently a toxic somatic fraction, also caused death within 24 hours of injection. Susceptibility of mice to this lethal effect was also increased by mucin and by adrenalectomy, and decreased by giving Cortisol.

These findings suggest to the authors that the condition of the host will affect resistance to *Staph. aureus* infection in a manner dependent on the strain of *Staph. aureus* used, and that endotoxin may be responsible for deaths occurring within 24 hours of infection.

J. W. G. Smith

Lambina, V. A. **[Induction in Staphylococci of Resistance to Streptomycin, Rivanol and Copper by means of Cell-Free Extracts]** *Mikrobiologiya.* Moscow. 1961, v. 30, No. 1, 60–66. [In Russian.] English summary.

Cell-free extracts were prepared from strains of *Staphylococcus aureus* which had been rendered resistant to streptomycin, rivanol and copper by growth in the presence of increasing concentrations. The washed bacterial mass was stood in contact with 70% ethanol for 24 hours at 4°C.; the alcohol was then removed and the cell residue was broken up by shaking with an equal volume of powdered glass and extracted with saline for 48 hours at 4°C. The extract after clarification by centrifugation was added to an equal volume of a broth culture of the sensitive original strain of *Staph. aureus*; after incubation for 24–72 hours a subculture was made on solid media containing rivanol, streptomycin or copper sulphate in order to find resistant variants. In this way the number of streptomycin-resistant organisms was increased from the proportion of $2{\cdot}3 \times 10^{-9}$, characteristic of the initial strain, to $4{\cdot}0 \times 10^{-2}$. It was similarly found that the proportions of individuals in the original strain resistant to rivanol and to copper were increased 400-fold and 20,000-fold respectively by growth in the presence of cell-free extracts of strains rendered resistant to the same substances. It was also possible to transfer resistance to 2 compounds sumultaneously.

D. J. Bauer

Wahl, R. & Fouace, J. Mutations d'une souche a *Staphylococcus aureus* vers le résistance à l'érythromycine avec perte de prophages. **[Mutations of a Strain of *Staphylococcus aureus* towards Erythromycin Resistance with Losses of Prophages]** *Ann. Inst. Pasteur.* 1961, May, v. 100, No. 5, 553–68.

A strain of *Staphylococcus aureus*, when grown in the presence of erythromycin, yielded resistant variants. Resistance to 100 μgm. per ml. was achieved in 2 steps. The original sensitive strain was shown to carry 2 different prophages, one of which was lost in each of the mutations to resistance. This prophage loss was accompanied by increase in sensitivity to several other phages. When the 1st mutant was lysogenized with the phage lost at the 1st mutation, the strain not only became resistant to the phage, but also reverted to full sensitivity to erythromycin. The resistance to 100 μgm. per ml. erythromycin could not be removed by lysogenization with the phage corresponding to the second prophage, though the appropriate phage resistance was achieved.

R. E. O. Williams

Maccabe, A. F., Gould, J. C. & Forfar, J. O. **Erythromycin-Resistant *Staphylococcus aureus*.** *Lancet.* 1961, July 1, 7–9, 1 fig. [14 refs.]

Investigations into the spread of an erythromycin-resistant strain of *Staphylococcus aureus* through a 400-bed general hospital in Edinburgh are described.

Between July 1958 and October 1959 1·7% of 1,681 strains from lesions were resistant to erythromycin, but 11·3% of 840 lesion strains isolated between November 1959 and August 1960 were resistant to this antibiotic, the greatest number being from the maternity and paediatric departments. The only 2 resistant strains from out-patients were from breast abscesses which may have been contracted in hospital.

Of the 2,521 strains, 27% belonged to phage Group I, 5% to Group II and 56% to Group III. 112 of the 122 erythromycin-resistant strains were of phage type 75/76/77. There were 2 minor and one more serious epidemic due to strains of this type during the period of study.

Staphylococcal air counts taken in various departments in September 1959 and October 1960 were not abnormally high and showed little difference between the 2 samplings and the various departments, but during the latter part of the study many erythromycin-resistant strains were isolated from swabs of fomites and from healthy carriers.

M. Patricia Jevons

Pan, Yue-Liang & Blumenthal, H. J. **Correlation between Acid Phosphatase and Coagulase Production or Phage Type of *Staphylococcus aureus*.** *J. Bacteriology.* 1961, July, v. 82, No. 1, 124–9, 1 fig. [25 refs.]

Wolfe, M. D., Cameron, G. M. & West, Mary E. **Further Observations on the Fluorescent Antibody Technique as a Procedure for Detecting Group A Streptococci in Throat Cultures.** *Pub. Health Lab.* 1960, Nov., v. 18, No. 6, 120–26.

2,719 throat cultures were examined for the presence of Group A streptococci by utilizing both the fluorescent

antibody technique and routine culture methods. The results of the two methods were in agreement in 2,453 (90·2%) of the specimens. 925 specimens were found positive by either method and of these 856 were positive by the fluorescent antibody technique and 728 by routine culture. In a further similar investigation the fluorescent antibody technique was utilized in a hospital laboratory by an individual who had a minimum of training in the fluorescent technique. The results on 116 submitted specimens were reasonably comparable with those obtained in the previous study. [Previous report; *Pub. Health Lab.* 1959, v. 17, 76. Similar studies, this *Bulletin*, 1958, v. 33, 1083 and 1961, v. 36, 927.]

H. Gooder

Smith, E. E. B., Mills, G. T. & Bernheimer, Harriet P. **Biosynthesis of Pneumococcal Capsular Polysaccharides. I. Properties of the System Synthesizing Type III Capsular Polysaccharide.** *J. Biol. Chem.* 1961, Aug., v. 236, No. 8, 2179–82, 5 figs.

Firshein, W. **Effects of Deoxyribonucleic Acid Products on Deoxyribonucleic Acid Synthesis of Virulent and Avirulent Pneumococci.** *J. Bacteriology.* 1961, Aug., v. 82, No. 2, 169–80, 8 figs. [31 figs.]

Firshein, W. **Effects of Deoxyribonucleic Acid Products on Respiration of Virulent and Avirulent Pneumococci.** *J. Bacteriology.* 1961, Aug., v. 82, No. 2, 181–6, 3 figs.

Viallier, J. & Lanery, R. Sur l'activité catalasique des mycobactéries. [**The Catalase Activity of Mycobacteria**] *C.R. Soc. Biol.* 1960, v. 154, No. 12, 2207–8.

All the atypical acid-fast bacilli and saprophytes that the authors have isolated have been catalase-positive in spite of being resistant to isoniazid, and 14 of the former strains were subcultured on Dubos medium containing 10 μgm. isoniazid per ml. every 21st day for 1 year and then retested for catalase. All the 10 chromogens had retained their activity but the 4 non-photochromogens had become catalase-negative. The peroxidase activity of these strains was also investigated by incubating suspensions in 0·15% hydrogen peroxide for 2½ hours at 37°C. and then subculturing dilutions of the suspension on to Löwenstein media. The number of colonies growing from the chromogenic strains was similar to those growing from suspensions not exposed to the peroxide, but the numbers growing from the non-photochromogens that had lost their catalase activity were much reduced.

Thus, although the catalase activity of the tubercle bacilli would appear to be different from that of the atypical bacilli, the difference would appear to be less marked with the non-chromogens. *S. R. M. Bushby*

Arima, J., Yamamoto, K. & Morikawa, K. Virulence des mycobactéries dites atypiques mesurée par la méthode de culture de tissu. [**Virulence of the So-called Atypical Mycobacteria measured by the Tissue Culture Method**] *C.R. Soc. Biol.* 1960, v. 154, No. 12, 2404–7.

The ability of 6 photochromogens, 8 non-photochromogens, 6 scotochromogens and 1 rapid-grower to multiply in tissue cultures of the spleens of guineapigs inoculated 3 days previously with 1 mgm. of the strains was compared with their virulence in mice and guineapigs. The technique previously described [this *Bulletin*, 1961, v. 36, 291] was used for the tissue cultures, the number of bacilli growing in the cultures being determined after 3 days' incubation. The virulence for the mice was assessed by the number of bacilli present in the lungs 7 weeks after intravenous injection of 10^{-7} viable units, and in guineapigs it was assessed by the extent of the disease and the number of bacilli present in the spleen.

None of the strains multiplied to any great extent in the spleen cultures although 1 photochromogen and 3 non-photochromogens increased somewhat more than did the others. In the guineapigs none of the strains produced progressive disease, but 2 of the non-photochromogens that showed the slightly higher multiplication in the spleen culture, produced lesions at the site of inoculation. None of the strains caused deaths of the mice but 8 showed moderate multiplication in the lungs.

The authors consider that these results are a further illustration of the value of the tissue culture method for assessing virulence of mycobacteria. *S. R. M. Bushby*

Thomas, J. P., Baughn, C. O., Wilkinson, R. G. & Shepherd, R. G. **A New Synthetic Compound with Antituberculous Activity in Mice: Ethambutol (Dextro - 2,2′ - (Ethylenediimino) - Di - 1 - Butanol).** *Amer. Rev. Respiratory Dis.* 1961, June, v. 83, No. 6, 891–3.

This substance, one of a numerous series synthesized and examined following the observation of antituberculous activity in N,N'-diisopropylethylenediamine, is a white crystalline substance highly soluble in water. *In vitro* it inhibits all mycobacteria studied in concentrations of 1–4 μgm. per ml., but has no action on other bacteria, fungi or viruses. Tubercle bacilli resistant to streptomycin or isoniazid are sensitive, and they do not develop significant resistance to ethambutol when exposed to graded concentrations in culture. Administered orally it attains a maximum level in the serum in 1 hour and is "rapidly excreted". Lethal doses for mice are very large. Mice infected with *Mycobacterium tuberculosis* H37Rv and with strains resistant to streptomycin or isoniazid were treated by either the oral or the subcutaneous route, with results from daily doses of the order of 200 mgm. per kgm. equal to those obtainable by the treatment of a sensitive infection with streptomycin or isoniazid.

Although large doses are required, the lethal dose of ethambutol is so high that its therapeutic index (ratio of toxic to effective dose) is about the same as that of

isoniazid and higher than that of streptomycin. [All these therapeutic tests were done with a mixture of the D- and L-isomers of this compound. It was subsequently found that the L-isomer is therapeutically inert, and the name ethambutol refers to the D-isomer.]

L. P. Garrod

BASTARRACHEA, F., ANDERSON, D. G. & GOLDMAN, D. S. **Enzyme Systems in the Mycobacteria. XI. Evidence for a Functional Glycolytic System.** *J. Bacteriology.* 1961, July, v. 82, No. 1, 94–100, 1 fig. [36 refs.]

SPITZNAGEL, J. K. **Macromolecule Synthesis in Long Forms of *Mycobacterium bovis* induced by Sulfate Deficiency.** *J. Bacteriology.* 1961, June, v. 81, No. 6, 933–8, 4 figs. [16 refs.]

HANKS, J. H. **Capsules in Electron Micrographs of *Mycobacterium leprae*.** *Internat. J. Leprosy.* Wash. 1961, Jan.–Mar., v. 29, No. 1, 84–7. [12 refs.]

A brief summary of the literature.

PAVLOV, P. V., LEONOVA, A. G. & SMIRNOVA, M. V. **The Influence of Products of Advanced Hydrolysis of Proteins of the Nutrient Medium on Toxin Formation by *C. diphtheriae*. I. A Medium digested with a Mixture of Trypsin and Enterokinase for the Preparation of Diphtheria Toxin.** *J. Microbiol., Epidemiol. & Immunobiol.* London. 1960, v. 31, No. 8, 1463–8, 1 fig. [Translated from Russian.]

Using the Weissensee variant of the Park-Williams-8 strain and a medium containing 0·4% maltose, the authors obtained high initial values of Lf toxin (65–120 Lf/ml.) in the primary cultures in a broth prepared with an emulsion of hog pancreas and duodenal mucous membrane so as to obtain the digestive effect both of trypsin and enterokinase on the meat. Paper chromotography suggested that these broths were particularly rich in a wide range of amino acids and contained proline and an unknown component in addition to those found in the other toxin-producing media in common use, such as that of Pope.

J. W. McLeod

MASHILOVA, G. M. **Study of the Redox Activity of *Corynebacterium diphtheriae*. II. The Catalase Activity of Toxigenic and Non-Toxigenic Strains.** *J. Microbiol., Epidemiol. & Immunobiol.* London. 1960, v. 31, No. 10, 1790–95, 2 figs. [11 refs.] [Translated from Russian.]

"(1) A definite relation has been discovered between the toxigenicity of strains of *Corynebacterium diphtheriae* and their catalase activity.

"(2) The highest catalase activity was found in toxigenic strains of *C. diphtheriae*, whereas non-toxigenic strains of *C. diphtheriae* and diphtheroids possessed little such activity."

J. APPLIED BACT. 1960, Dec., v. 23, No. 3, 373–537, illustrated. [Numerous refs.] **Symposium on *Pseudomonas* and *Achromobacter*.**

The organizers of this Symposium made sure that both speakers and listeners knew what organisms were being discussed, and several of the opening papers were devoted to the problems of classification and identification. M. INGRAM and J. M. SHEWAN (pp. 373–378) traced the history of the separation of *Pseudomonas* and *Achromobacter* and J. M. SHEWAN, G. HOBBS and W. HODGKISS (pp. 379–390) put forward a scheme of classification which depended on the behaviour of the organism in HUGH and LEIFSON glucose medium [this *Bulletin*, 1954, v. 29, 83], the production of diffusible pigment, sensitivity to penicillin and to the pteridine compound 0/129, the oxidase reaction, and the type of flagellation. A. J. HOLDING (pp. 515–525) described the Gram-negative bacteria from soil and the characteristics of the genera found, which in large measure agreed with those of Shewan *et al.* for organisms from marine sources [a table combining these distinguishing characters, prepared by the abstracter, is shown below].

Table showing main distinguishing features of the Gram-negative rods found in food and soil.

	Motility	Flagella	Pigment	Glucose	Oxidase	Mineral** N
Pseudomonas ...	+	Polar	+(*)	O	+	+
Ps. (non-pigmented)	+	Polar	–	–	+	+
Achromobacter ...	–	–	–	O	–	–
Alcaligenes	–	–	–	–	–	+
Flavobacterium ...	–	–	+	O	–	–
Cytophaga	–	–	+	O	–	+
Vibrio	+	Polar	–	F	+	
Aeromonas	+	Polar	–	FG	+	

O = oxidized
F = Fermented
G = Gas produced
(*) = pigment is diffusible
** = Growth on medium containing mineral Nitrogen as only source of N.

W. HODGKISS (pp. 398–399) stressed the difficulties encountered in interpreting what is seen in preparations stained to show flagella. A flagellum approximately 200 Å wide has to be thickened to become visible in the optical microscope, and controls of polar and peritrichous organisms should always be included.

K. KLINGE (pp. 442–462) discussed the tests used to distinguish species and pointed out that the results of the oxidase test might depend on the reagent and the media used. Although Bergey's *Manual* lists 149 species of *Pseudomonas*, all speakers were agreed that only a much smaller number (3 to 11) could be clearly distinguished.

When freshly caught, fish were eviscerated, washed and packed in ice and J. M. SHEWAN, G. HOBBS and W. HODGKISS (pp. 463–468) made bacterial counts of the skin of fish stowed in Aberdeen trawlers at 0–1·5°C. for up to 20 days. At first pseudomonads, achromobacters and coryneforms were present in about equal numbers

but during storage the pseudomonads increased much more than the achromobacters while the coryneforms decreased. J. Liston (pp. 469–470) had similar results from fish caught in the Pacific.

J. C. Ayers (U.S.A.) (pp. 471–486), M. J. Thornley, M. Ingram and E. M. Barnes (U.K.) (pp. 487–499) and J. Brooks (U.K.) (pp. 499–519) reported on the bacterial flora of poultry and eggs. Psychrophils (defined as organisms able to grow to visible colony size in 14 days at 1°C.) in dressed poultry increased 1,000-fold before the first trace of odour was noticed, but a further 10-fold increase made the carcase smell strongly. Storage resulted in an increase in the number of non-pigmented pseudomonads (in the past often recorded as achromobacters). Tetracyclines added to the ice slush extended the storage life but yeasts, achromobacters and pigmented pseudomonads then increased. Bacteria only penetrate the eggshell when it is wet, and after penetration have to get through two shell membranes to reach the white. White of egg is not a good growth medium for bacteria, it has a *p*H of about 9 and is deficient in iron.

Pseudomonads, particularly *P. aeruginosa* [*pyocyanea*] may contaminate and multiply in stored blood. They may also cause hospital infections, several of which are described by K. B. Rogers (pp. 533–537), who gives details of the methods he uses for their isolation. *Ps. aeruginosa* grows on most media used in medical laboratories, including MacConkey and deoxycholate-citrate agar. *S. T. Cowan*

Dolby, Jean M., Thow, Doraine C. W. & Standfast, A. F. B. **The Intranasal Infection of Mice with *Bordetella pertussis*.** *J. Hygiene.* 1961, June, v. 59, No. 2, 191–204, 9 figs. [13 refs.]

When *Bordetella pertussis* in introduced intranasally into the mouse it will proliferate in the respiratory tract. To kill the mouse, however, a sufficiently large dose must be given as otherwise the organisms cannot outstrip the development of immune defence mechanisms. The authors traced the course of infection with sublethal and lethal doses of several strains by means of lung counts and found that the mice died if the count reached the critical number of 10^8 within 10–14 days.

Two antibodies are related to the immunity of mice to *B. pertussis*: one confers protection against a lethal challenge by the intranasal route, the other against intracerebral infection. Provided intranasal antiserum was brought into direct contact with the organisms (by administration at the time of, or after, but not before, their intranasal installation), it rapidly reduced the count to sublethal numbers. Active immunization also produced a sharp reduction in the lung counts. The effect was more prolonged and a proportion of the lungs became sterile much earlier than with a sublethal infection in an unprotected animal.

The presence of complement was necessary for the *in vitro* reduction of the viable count of *B. pertussis* by intranasal antiserum. The authors suggest that the *in vivo* activity of the antiserum is due to the complement present in the lung exudate. *J. M. Stark*

Dolby, Jean M. & Standfast, A. F. B. **The Intracerebral Infection of Mice with *Bordetella pertussis*.** *J. Hygiene.* 1961, June, v. 59, No. 2, 205–16, 10 figs. [17 refs.]

The intracerebral inoculation of mice with virulent strains of *Bordetella pertussis* resulted in a lethal infection no matter how small the dose. After an initial sharp fall due to spill-over into the bloodstream, the characteristic viable count rose at a constant rate, unrelated to inoculum size, until a critical number (about 10^8) was reached, at which the animal died.

Passively or actively immunized animals survived but the counts did not begin to drop until the 4th day after infection. This corresponded in time with the breakdown of the blood-brain barrier by local inflammatory damage which allowed the circulating antibody to come in contact with the organisms. *J. M. Stark*

Standfast, A. F. B. & Dolby, Jean M. **A Comparison between the Intranasal and Intracerebral Infection of Mice with *Bordetella pertussis*.** *J. Hygiene.* 1961, June, v. 59, No. 2, 217–29, 7 figs. [16 refs.]

Reviewing their own work and that of others, the authors describe the course of intranasal and intracerebral infection with *Bordetella pertussis* in mice. They extend this with further studies which showed that the animals were much more susceptible to the action of toxic extracts administered intracerebrally than to those given intranasally, although the infection experiments had shown the terminal counts in brain and lung to be remarkably similar (about 10^8). Death from already established infection at one site was not hastened by superadded infection at the other.

Previous work was confirmed which showed that the intracerebral antibody is effective in controlling sublethal (but not lethal) intranasal infection. The authors emphasize, however, that as intranasal antibody also protects against sublethal intranasal infection this does not distinguish the two. [The distinction is worthwhile for it is the intracerebral antigen which is related to the most satisfactory immunization of children.]

The authors go on to discuss the various differences in the two modes of infection already outlined in their two previous papers [see above]. *J. M. Stark*

Howard, J. G. **Resistance to Infection with *Salmonella paratyphi C* in Mice parasitized with a Relatively Avirulent Strain of *Salmonella typhimurium*.** [Correspondence.] *Nature.* 1961, July 1, v. 191, 87–8. [16 refs.]

It was shown by Hobson [this *Bulletin*, 1958, v. 33, 164] that mice surviving experimental infections with a relatively avirulent strain of *Salmonella typhi-murium*, but still carrying the organism were resistant to a subsequent superimposed infection with a virulent strain of *Salm. typhi-murium*. In a similar type of experiment the present author found that mice parasitized with the same relatively avirulent strain of *Salm. typhi-murium* (S2/R)

were resistant to a superimposed infection with a heterologous salmonella organism—the virulent East African (Kauffmann) strain of *Salm. paratyphi C*. The antigenic relationship between *Salm. typhi-murium* and *Salm. paratyphi C* is of a very minor order—the common H-factor 1 only—and careful cross-testing fails to show any O antigenic relationship between the two organisms. The findings indicate that there is a considerable non-specific element which is responsible for this resistance to the superimposed infection. It is suggested that the previously induced parasitization of the reticulo-endothelial cells with the avirulent strain of *Salm. typhi-murium* blocks or prevents, in some way, the subsequent multiplication of the secondarily introduced virulent, but unrelated, culture.

[These observations are of considerable interest but a satisfactory explanation is not obvious and it is not clear how much the results observed depend on the doses of organisms used in the experiments. Further investigations on the same lines are clearly desirable.] In the experiments reported the mice were originally infected with 1,000 bacteria of the S2/R strain of *Salm. typhi-murium* and 13 days later the total bacterial counts in samples of the parasitized mice were between 10,000 and 50,000 bacterial cells. The following day the remaining mice were each given 100,000 *Salm. paratyphi C* intravenously. Only 1/20 of the test mice died with a *Salm. paratyphi C* bacteraemia and all the 20 control mice died from the paratyphoid C infection. *H. J. Bensted.*

Springer, G. F., Williamson, P. & Brandes, W. C. **Blood Group Activity of Gram-Negative Bacteria.** *J. Exper. Med.* 1961, June 1, v. 113, No. 6, 1077–93. [40 refs.]

The authors have examined the distribution of blood group A, B, and H(O) activities among the aerobic Gram-negative bacteria, including the *Escherichia, Salmonella,* Arizona, *Klebsiella, Citrobacter, Proteus, Pseudomonas, Serratia, Herrellea, Alkaligenes* and *Pasteurella.* Out of some 280 organisms examined about half exhibited some degree of activity, a significant proportion having high activity which in some cases approached that of crude human blood group mucoids. The most commonly observed blood group specificities were H(O) (against eel serum) and B, either alone or in combination; they predominated in all genera which contained active strains. Bacteria with a single specificity far outnumbered those with 2 or 3 blood group activities.

A, B, and H(O) blood group activities were not confined to any particular genus of Gram-negative bacteria, but it is noteworthy that different species of salmonellae possessing the same major O antigens showed the same blood group activities; these could be correlated, in the particular case of salmonellae with the O antigen formula 13·23, with their monosaccharide components. Attention is also drawn to the fact that many of the Gram-negative bacteria with these human blood group activities are frequently associated with human infections, mainly intestinal in nature but some may be isolated from the blood. *H. J. Bensted.*

Nicolle, P., Nicolle, J. & Diverneau, Gisèle, with the technical collaboration of Anne M. Du Plessis & Joëlle Coignard. Recherches sur le comportement fermentatif des bacilles typhiques à l'égard du xylose naturel D(+) et de son inverse optique L(−). **[Studies on the Fermentative Behaviour of Typhoid Bacilli towards Natural D(+) Xylose and its Optical Inverse L(−) Xylose]** *Ann. Inst. Pasteur.* 1961, Aug., v. 101, No. 2, 211–23, 2 figs. [23 refs.]

The classification of *Salmonella typhi* into sub-types in accordance with their fermentation ability in respect of xylose and arabinose was suggested by Kristensen and Henriksen in 1926 (*Acta Path. et Microb. Scandinavica,* 1926, v. 3, 551) and the method has been extensively studied by the senior author (*Rev. Française Etudes Clin. et Biol.*, 1957, v. 2, 929) who favoured the classification which depended only on the fermentation of xylose.

The present paper reports the examination of nearly 10,000 strains of *Salm. typhi* from various countries in four continents with regard to their fermentation of D(+) xylose. 72·9% of the total number fermented D(+) xylose (Kristensen's chemotype I) and 27% failed to attack it (chemotype II). When strains from separate geographical areas were examined there was considerable differences in the proportion of chemotypes I and II; in Vietnam and Cambodia over 80% of the strains belonged to chemotype I whereas in Senegal the percentage was only a little over 50. When the test was considered in relation to the Vi antigen and sensitivity to the various Vi phages it was found that in most cases the strains were biochemically homogeneous so that the biochemical method of classification could only offer confirmatory information to that obtained by phage typing. On the other hand there were some phage types in which some strains belonged to chemotype I and others to chemotype II and for these the fermentative activity of the strains on D(+) xylose could be used as a further epidemiological tool.

After conducting a number of experiments with strains belonging to chemotype I in which L(−) xylose replaced the natural D(+) xylose, but with negative results, it was concluded that the enzyme system of the typhoid bacillus which attacks D(+) xylose has no activity against L(−) xylose and that the organism had no enzyme system able to attack L(−) xylose.

H. J. Bensted

Mithal, S., Barua, D. & Aikat, B. K. **The Effect of Chloramphenicol on the Antigenicity and Agglutinability of *S. typhi* and on the Antibodies.** *Indian J. Med. Res.* 1961, May, v. 49, No. 3, 357–67. [13 refs.]

This and the succeeding paper, from Calcutta, describe experiments to elucidate the supposed impairment of the immune response in typhoid fever by treatment with chloramphenicol, as evidenced mainly by the frequency of relapse. Here only some rather unlikely possibilities are excluded. By immunizing groups of rabbits with typhoid bacilli, variously treated, and measuring their

agglutinin response (H and O) it was shown that either a short exposure to chloramphenicol, or actual growth (after training) on medium containing 10μgm. per ml. did not alter the antigenicity of the bacilli: the only demonstrated effect of such training was some loss of Vi-agglutinability. It was also shown that treatment of rabbits with chloramphenicol for 7 days after immunization did not reduce the agglutinin content of the blood, and that incubation of serum with chloramphenicol for 1 week did not reduce its titre. *L. P. Garrod*

BARUA, D., MITHAL, S. & AIKAT, B. K. **Rôle of Chloramphenicol on the Development of Immunity in Infection by *S. typhi*.** *Indian J. Med. Res.* 1961, May, v. 49, No. 3, 368–87. [30 refs.]

In similar experiments to the foregoing it was first shown that administration of chloramphenicol to rabbits during immunization does not depress the formation of H and O agglutinins for *Salmonella typhi*. There was also no effect on the resulting H, O and Vi titre when 3 doses of living organisms were used for immunization. On the other hand, when a single intravenous injection of 100 cells of *Salm. typhi-murium* was given, H titres of 160–320 and O of 20–80 were attained in untreated animals, whereas in those treated wtih chloramphenicol the titre was usually *nil*. Here some clinical data are interposed showing lack of correlation of agglutinin titres with the stage of the disease at which chloramphenicol treatment was begun. Finally some experiments in mice are described: these animals were inoculated with 25 *Salm. typhi-murium* and three-quarters were treated with chloramphenicol, which increased the survival rate. On re-inoculation of the survivors with 12,500 organisms the mortality was higher in mice previously treated with chloramphenicol.

Some results of passive protection tests in mice with sera from immunized rabbits are also reported, which only confirm that chloramphenicol treatment during immunization does not interfere with the response. In discussion the authors emphasize the variations in the rate of immune response in patients with typhoid fever, and suggest that chloramphenicol treatment may predispose to relapse in "slow reactors". *L. P. Garrod*

PONTECORVO, M. **The Effect of Typhoid Vaccine of Different Quality on the Antigenic Efficiency of Tetanus Toxoid.** *Riv. Istituto Sieroterap. Ital.* 1961. Mar.–Apr., v. 36, No. 2, 121–7. [14 refs.]

Previous experiments by BARR with mixtures of tetanus toxoid and TAB vaccine [this *Bulletin*, 1956, v. 31, 993] indicated that the antigenic quality of a toxoid plays an important part in determining whether synergy or a reduced response will follow the injection of mixtures of the toxoid with another antigen. In the present paper the author re-examines the problem by studying the immune response of guineapigs to the same batch of tetanus toxoid in combination with 11 different typhoid vaccines. Although it was confirmed that antitoxin production in animals receiving toxoid together with typhoid O and Vi antigens was significantly greater than in animals receiving toxoid only there was little evidence to show that this increase was directly related to the potency of the typhoid vaccine used (as judged by the chick protection test), but rather that it depended in the main on the polysaccharide content of the vaccine. In this connexion it is of interest to note that the combined preparation containing the typhoid vaccine made from the relatively avirulent strain 0–901 resulted in an antitoxic level which was higher than was obtained with some vaccines made from the fully virulent O Vi strain Ty2. Nevertheless it seems possible that the various chemical and physical agents employed for killing and preserving the typhoid vaccine could influence the antigenic response to the tetanus toxoid and these possibilities are discussed. *H. J. Bensted*

See also p. 1223, PUBLIC HEALTH LAB. SERVICE, **The Detection of the Typhoid Carrier State. Report of the PHLS Working Party on the Bacteriological Examination of Waterworks Employees.**

SMITH, C. G. **Deoxyribokinase in *Salmonella schottmuelleri*.** *J. Bacteriology.* 1961, Feb., v. 81, No. 2, 328–9, 1 fig.

KALLE, G. P. & GOTS, J. S. **Antagonisms between Purines and Purine Analogues in Auxotrophs of *Salmonella typhimurium*.** *J. Bacteriology.* 1961, Mar., v. 81, No. 3, 331–7, 5 figs. [18 refs.]

RAETTIG, H. & WÖLK, Brigitte. Provokation einer Infektion durch Schutzimpfung. VI. Mitteilung. Leukocytenwerte nach subcutaner Immunisierung der Maus. [**Promotion of Infection by Prophylactic Immunization. VI. Variation of Leucocyte Count consequent on Subcutaneous Immunization of Mice**] *Zent. f. Bakt.* I. Abt. Orig. 1961, v. 182, No. 3, 294–17, 13 figs [36 refs.]

This is a further instalment in a series of studies of the phenomenon of promotion of infection by "protective" inoculation in the period of incubation of the infection [this *Bulletin*, 1960, v. 35, 1145].

The leucocytic response to injections of *Salmonella typhi-murium*, poliomyelitis vaccine and adjuvants such as aluminium hydroxide has been investigated in the mouse. It is pointed out that the results can only be applied to parallel happenings in man with reservations in view of the differences in equipment with leucocytes. The total number of leucocytes is 50% greater in the rodents and the relative numbers of lymphocytes and polymorphs is the mirror-image of that in man. Besides this the cells rare in human blood such as mast cells appear to be absent from the blood of the mouse.

The general outcome of these observations is to indicate a limited temporary leucopenia 5–12 hours after injection of any of the materials mentioned above but most marked with the salmonella vaccine. This fall is entirely due to a diminution of lymphocytes since it

occurs notwithstanding a moderate rise in the polymorphonuclear forms.

The possible significance of this drop in lymphocytes is discussed at length and the authors suggest that it indicates a weakening of the defence mechanism although they admit that no exact knowledge of the role of the lymphocyte is yet available. This cell is humorously described as the "*bête noire*" of the haematologists.

J. W. McLeod

MORRIS, B. **The Transmission of Anti-*Salmonella* Agglutinins from the Mother to the Young in *Erinaceus europaea*, with some Observations on the Active Immunization of Suckling Hedgehogs.** *Proc. Roy. Soc.* Ser. B. 1961, July 25, v. 154, No. 956, 369–76. [12 refs.]

If pregnant hedgehogs are actively immunized with a *Salmonella pullorum* vaccine they transmit specific passive immunity to their young before birth and it seems probable that the route of transfer before suckling is the allantochorionic placenta. As soon as suckling commences this passive immunity is augmented by the uptake of antibody from the milk by the gut, which continues for about 30 days. In the experiments described in this paper it was found, for example, that the immunized mother at the time of the birth of a litter might have a *Salm. pullorum* agglutinin titre of 1 in 5,000 in her serum and 1 in 2,500 in her milk whereas the young at birth, before suckling, would have a serum titre of 1 in 160—a concentration quotient of 1/32. During the first 20 days of lactation the concentration quotient might be from 1/4 to 1/2; thereafter the serum titres of the young would decline. In the mother the serum titre was about twice the titre found in her milk, but the uptake of antibody in the young from the milk was at a very much lower level.

Generally the ability of the young mammal to produce its own circulating antibodies in response to injection of antigen is not developed until its passively acquired immunity is waning. In the young suckling hedgehog, however, a single injection of *Brucella abortus* vaccine at the ninth day after birth will result in the development 6 days later, of detectable, though low antibody titres. It is of interest to note that pregnant hedgehogs immunized with a brucella vaccine may have brucella agglutinins ranging from titres of 1 in 160 to 1 in 1,280 but there is no transfer of antibodies to this organism to the young prenatally, and the post-natal transfer is of a very low order.

H. J. Bensted

LE MINOR, L., LE NOC, P., DREAN, D. & CHARIE-MARSAINES, C. Quatre nouveaux sérotypes de *Salmonella*. **[Four New *Salmonella* Serotypes]** *Bull. Soc. Path. Exot.* 1961, Mar.–Apr., v. 54, No. 2, 164–6.

The 4 new serotypes were: Salm. Sakaraha (48:K:*z* 39); Salm. Antsalova (51:*z*:1,5); *Salm. Soahanina* (6,14,24:*z*:*enx*); Salm. Foulpointe (38:*gt*).

All were from reptiles.

BRYGOO, E. R. & LE NOC, P. Note préliminaire sur les salmonelles des caméléons malgaches. **[Preliminary Note on Salmonellae in Malagasy Chameleons]** *Bull. Soc. Path. Exot.* 1961, Mar.–Apr., v. 54, No. 2, 166–9.

The English summary appended to the paper is as follows:—

"The authors describe the first results of an epidemiological survey on the intestine flora of chameleons. They have isolated 13 strains of *Salmonella* belonging to 12 different serotypes. The part played by chameleons in the propagation of human salmonellosis is pointed out."

STOKES, J. L. & BAYNE, H. G. **Oxidative Assimilation of Amino Acids by Salmonellae in relation to Growth Rates.** *J. Bacteriology.* 1961, Jan. v. 81, No. 1, 118–25, 1 fig. [17 refs.]

BAYNE, H. G. & STOKES, J. L. **Amino Acid Metabolism of Salmonellae.** *J. Bacteriology.* 1961, Jan., v. 81, No. 1, 126–9, 1 fig. [12 refs.]

LACHOWICZ, T. M., MULCZYK, M. & ROWINSKI, S. **Further *in vitro* Studies on the Mechanism of Selection among Serological *Shigella flexneri* Types.** *Archiwum Immunol. i Terapii Dośw.* Warsaw. 1961, v. 9, No. 1, 69–76, 1 fig. [11 refs.]

In a previous paper these authors [see MULCZYK and LACHOWICZ, this *Bulletin*, 1961, v. 36, 805] have shown that during subculture procedures of a culture of *Shigella flexneri*, comprising a mixed population of subtype 1b and its mutant, a serological variety of type 3, selection favoured the mutant under the conditions of the experiment. It was suggested that the selecting agent might either be a latent phage or an agent of the colicine type.

In the further investigations reported in the present paper, streptomycin-resistant mutants were obtained from both the streptomycin-sensitive strains *Sh. flexneri* 1b and the serological variety type 3. In mixed populations of the streptomycin-resistant mutants the selection of type 3 takes place, no matter what proportions of the two are in the initial population, but the lower the percentage of type 3 in this mixture the later in the serial passage is their predominance in the medium established. But when the mixed populations consisted of streptomycin-sensitive and streptomycin-resistant strains the results were even more interesting: the streptomycin-sensitive strain was always the dominant form. For instance, mixtures of the sensitive 1b and the resistant type 3 strain showed that the streptomycin-sensitive 1b strain was dominant and there appeared to be no selection of the type 3 forms after 5 passages. After a reasonable discussion the authors conclude that the results obtained were probably not due to the effect of temperate phage but were more likely due to the Welsch phenomenon. However, further work was indicated.

[There are comparatively few references to the "Welsch phenomenon" in the literature, especially in

journals printed in the English language, and it may be of interest to recall that WELSCH (*C. R. Soc. Biol.*, 1949, v. 143, 1282) found that successive subcultures of mixtures of streptomycin-sensitive and streptomycin-resistant *Staphylococcus aureus* in streptomycin-free broth cultures resulted in the emergence, after various numbers of culture-transfers, of more or less pure cultures of the streptomycin-sensitive strain which appeared to be the predominant form, while the streptomycin-resistant strain disappeared from the culture. At that time Welsch himself could offer no satisfactory explanation for the observations, but seemed to be satisfied that there was no significant difference in the multiplication rates of the streptomycin-resistant and the streptomycin-sensitive organisms. Welsch's findings were confirmed and found to be applicable to other organisms, but, as far as is known, the mechanism of the phenomenon remained unexplained until BANIC (this *Bulletin*, 1958, v. 33, 871) produced evidence to show that it depended on the fact that the normal antibiotic-sensitive bacterial strain multiplied more rapidly than the resistant mutant. In his experiments he used *Escherichia coli* B and mutants with different degrees of resistance to streptomycin and the Oxford standard strain of *Staph. aureus* as the penicillin-sensitive and artificially-induced resistant strains and also freshly isolated strains which were naturally resistant to penicillin. The results were substantially the same in all cases: the antibiotic-sensitive strain was the dominant strain; it grew more quickly than the resistant strain on solid media so that colonies of the same age were significantly larger in the case of the sensitive strain compared with those of the resistant strain. The difference in the multiplication rates of the sensitive and resistant strains in artificial mixtures of the two strains in broth cultures was readily demonstrated by the emergence after successive subcultures of almost pure cultures of the dominant antibiotic-sensitive strain, but the success of this procedure and the number of transfers necessary depended on the proportion of the two strains in the original mixture and the size of the inoculum. Banič's paper is not referred to by the authors of the article under review and since Banič quoted Welsch as saying: "Pure cultures of totally resistant organisms grow just as quickly and just as well as normal cultures . . .", there seemed to be some justification for this comment.]

H. J. Bensted

SCHUH, V. & KLECKOVÁ-ALDOVÁ, Eva. Sulfonamidorezistence shigel. I. Příprava tekuté půdy. [**Resistance of *Shigella* to Sulphonamides. I. Preparation of a Liquid Medium**] *Československ. Epidemiol., Mikrobiol., Imunol.* Prague. 1961, v. 10, No. 2, 102–10, 3 graphs. [21 refs.] English summary (3 lines).

The authors have developed a medium for testing the sulphonamide resistance of strains of *Shigella*, which is designed to be free from compounds which are non-competitive inhibitors of sulphonamides. 1 litre of the medium contains 10 gm. of casein acid hydrolysate, 5 mgm. of tryptophan, 0·2 gm. of dipotassium hydrogen phosphate, 5 mgm. of ferrous sulphate heptahydrate, 0·2 gm. of magnesium sulphate heptahydrate, 15 mgm. of nicotinic acid, 1 mgm. of thiamine, 1 mgm. of calcium pantothenate and 5 gm. of glucose. The *p*H is 7·2–7·4. By determining the resistance of a sensitive strain of *Sh. flexneri* in medium containing increasing amounts of the casein hydrolysate it could be shown that the presence of this constituent did not influence the results obtained, whereas the addition of peptone or liver infusion made the medium unsuitable for determinations of sulphonamide resistance.

D. J. Bauer

SERÉNY, B. Új eljárás *Sh. sonnei* tenyészetek vizsgálatára. [**A New Procedure for Investigating Cultures of *Shigella sonnei***] *Egészségtudomány.* Budapest. 1960, v. 4, No. 1, 1–10, 2 figs. [14 refs.] German summary.

By examining colonies of *Shigella sonnei* with a hand lens in incident light of varying obliquity 3 types of colony can be distinguished. (1) Stellate, in which a more refractile irregular star-shaped area can be distinguished against the general background of the colony; these are very frequent in freshly isolated strains, and the number of stellate colonies gradually decreases on subculture. (2) Homogeneous; 3 subgroups can be recognized among these colonies according to their degree of refractility. (3) Reticular; the colonies are marked with a network of lines. The various types of colony showed no differences in their enzymatic activity towards carbohydrates, but a close relationship was observed between colonial morphology and antigenic structure. Thus colonies containing only S antigen were homogeneous and highly refractile, whereas those containing only phase II organisms were homogeneous and less refractile; the former organisms constituted the star-shaped area of the stellate colonies, appearing against a background of phase II organisms.

D. J. Bauer

SZTURM-RUBINSTEN, Szymona & PIÉCHAUD, Danielle. Mode de propagation des bacilles dysentériques. I. Étude expérimentale chez le cobaye avec *Shigella sonnei*. [**Mechanism of the Propagation of Dysentery Bacilli. I. Experimental Study in Guineapigs inoculated with *Shigella sonnei***] *Ann. Inst. Pasteur.* 1961, Aug., v. 101, No. 2, 224–33.

In preliminary experiments with guineapigs inoculated intraperitoneally with cultures of Flexner or Sonne bacilli in doses of 0·5 ml. of a 24-hour broth culture it was found that in animals dying within 24 hours or killed at that time, the organism could be recovered from the blood and most of the lymph nodes, but animals surviving for the first 24 hours and killed at later times failed to show any evidence of bacteraemia and little evidence of glandular involvement. When the inoculations were given intradermally generalized glandular involvement was demonstrated as early as 6 hours after inoculation but there was no evidence of any bacteraemia until 3–4 days later when it was of a light nature only. These experiments were with phase I Sonne; phase II organisms appeared to be avirulent and viable bacteria were not recovered from the inoculation site, the blood or any of the lymph glands of animals killed from 6 hours onwards after inoculation. When measured doses

of phase I Sonne were given intradermally (10^7 organisms ranging down to 10^4) it appeared that the critical dose level was in the region of 10^5 organisms: above 10^5 there was bacteraemia and widespread glandular involvement and below this level the organism could not be recovered from the blood but there was a light infection of the glands after 24 hours.

[The authors conclude that these results suggest that in the guineapig Sonne infection spreads *via* the lymphatic system, but it may be felt that further controlled experimentation employing larger numbers of animals would be necessary before more definite conclusions would be justified. At the same time it is a little difficult to understand from experiments of this nature, which make no attempt to imitate the natural infection in man, the march of events in the human disease where, except in very severe infections, the condition is localized to the bowel with only slight involvement of the glands draining the affected area but without distal spread. Occasionally very severe cases may be seen in young infants in whom the infecting dose is presumably heavy and a bacteraemia may be demonstrated. These are not common, but the reviewer has knowledge of one or two such cases and recently, from Dakar, BAYLET reported the isolation of *Shigella sonnei* from the blood of a young infant severely ill with Sonne dysentery [this *Bulletin*, 1960, v. 35, 577].

During the First World War, among patients with severe Shiga and Flexner dysentery dying early on in the disease, it was not uncommon to find intense ulceration of the bowel with enlarged acutely inflamed mesenteric glands, but wider dissemination was very rare, although examples were said to occur. In connexion with involvement of the mesenteric glands in Shiga dysentery it is of interest to recall that over 70 years ago CHANTEMESSE and WIDAL (*Bull. Acad. Méd.*, Paris, 1888, v. 19, 522) cultured the organism of epidemic dysentery from the mesenteric glands and intestine of a patient dying of the disease. This was 10 years before SHIGA reported the isolation of the same organism (*Zent. f. Bakt.* I. Abt. Orig., 1898, v. 23, 599) which has, except in France, always borne his name until very recent years. Chantemesse and Widal's organism had, fortunately, been preserved and when VAILLARD and DOPTER re-examined it some 15 years later they found it to be identical with Shiga's bacillus (*Ann. Inst. Pasteur*, 1903, v. 17, 463). Had the original description by Chantemesse and Widal been more exact there is little doubt that the organism would have been given another name. Shiga's own description was not quite correct and it took KRUSE and almost a "Royal Commission" to establish the fact that the organism was not motile.] *H. J. Bensted*

SERÉNY, B. **Variants of *Sh. sonnei* Phase I.** *Acta Microbiologica.* Budapest. 1961, v. 8, No. 2, 159–72, 2 figs. [35 refs.]

This author has been studying *Shigella sonnei* intensively for several years and has published a number of papers relating to variation in colonial morphology and antigenic make-up and other characters of this interesting organism [this *Bulletin*, 1960, v. 35, 396 *bis* and 928] and much that is contained in the present article will be familiar to readers of his previous papers.

One of the variants described in this paper, designated 2b, which appears to have an antigen make-up comprising, almost exclusively, phase I antigen, was found to be avirulent for mice. This is contrary to most previous experience, which has been that cultures of *Sh. sonnei* rich in phase I antigen are highly virulent for mice. Pure phase II cultures are avirulent and mixtures of phases I and II have a virulence for mice in accordance with the proportions of phase I and phase II antigens occurring in the particular culture being tested. But some cultures, although predominantly phase I, may contain obvious amounts of phase II antigen and still be highly virulent for mice. The fact that phase I cultures may not always be virulent for mice was noted by PIÉCHAUD and SZTURM-RUBINSTEN [*ibid.*, 1960, v. 35, 301] and is fully confirmed by the detailed observations of the author of this paper. It is suggested, therefore, that the factor responsible for virulence does not necessarily form an integral part of phase I antigen.

H. J. Bensted

HUET, M., PAPAVASSILIOU, J. & BONNEFOUS, S. Recherches sur les *Shigella* colicinogènes. [**Colicine-Producing Shigellae**] *Arch. Inst. Pasteur de Tunis.* 1961, June, v. 38, No. 2, 109–19. [13 refs.]

This study of colicine production by the various members of the *Shigella* group for the purpose of finer differentiation than is offered by serological typing methods, known as colicinogenic-typing, is to be distinguished from colicinotyping by the fact that the latter indicates the typing of strains in accordance with their sensitivity to various colicines, whereas the former determines the type of colicine produced by a particular strain of a bacterial species. The actual method employed by the authors was a modification of the double layer technique of GRATIA which allowed up to 8 *Shigella* strains to be tested for colicine production. Those producing colicine which was active against the special Row strain of *Escherichia coli* were then individually tested against various mutants resistant to certain colicines in order to determine the type of the colicine produced by the strain under test. The specific inhibitors used corresponded to the colicines V, B, E, I and K which appear to be the FREDERICQ series [this *Bulletin*, 1949, v. 24, 805].

The majority of the 223 strains of shigellae examined were isolated from sporadic cases, but whereas the percentage of colicinogenic *Sh. dysenteriae* and *Sh. flexneri* was found to be very low, it was reasonably high in the case of *Sh. boydii, Sh. sonnei* and the Alkalescens-dispar group. It therefore appeared that colicinogenic typing of the commonest dysentery organism, *Sh. sonnei,* will prove to be a valuable epidemiological tool in the study of outbreaks of bacillary dysentery of the Sonne type, but the authors themselves were unable to obtain sufficient experience of this nature to substantiate this thesis.

[ABBOTT and SHANNON (this *Bulletin*, 1958, v. 33, 689; ABBOTT and GRAHAM, *ibid.*, 1961, v. 36, 1187) using a rather different method have also studied intensively the typing of *Sh. sonnei* by colicine production.]

H. J. Bensted

LIDWELL, O. M. & CARPENTER, K. Patricia. **Apparatus for Colicine Typing.** *Monthly Bull. Ministry of Health & Pub. Health Lab. Service (directed by Med. Res. Council).* 1961, June, v. 20, 119–20, 1 fig. & 1 pl.

This apparatus was devised for the main purpose of reducing some of the tedious work involved in typing *Shigella sonnei* strains in accordance with colicine production by the method described by ABBOTT and SHANNON [see this *Bulletin*, 1958, v. 33, 689; ABBOT and GRAHAM, *ibid.*, 1961, v. 36, 1187].

The essential piece of the apparatus is a system of vertically set nichrome wire loops, up to 9 in number, which can be individually charged with broth cultures of different colicine indicator strains at one and the same time and then streaked over the surface of an agar plate at right angles to the single streak culture, the surface growth of which has previously been scraped off, of the *Sh. sonnei* culture under test. The apparatus may be said, therefore, to be concerned with the application of inocula from stock cups of the 9 indicator-strain cultures in the correct order and approximately the same dose to a series of test culture plates of *Sh. sonnei*. This short note is accompanied by a photograph of the apparatus, as set up for use, and an explanatory diagram of the apparatus with notes beneath.

The authors have had considerable experience with the apparatus and there seems to be little doubt that in a laboratory where colicine typing of this sort is undertaken on a reasonably large scale the procedure described could mean a considerable saving of time.

H. J. Bensted

JUNGHANS, Ruth. Zur Zysotypie von *Shigella sonnei*. Die bisher gefundenen Lysotypen, ihre epidemiologische Verwertbarkeit und Stabilität. **[Phage-Typing of *Shigella sonnei*. Lysotypes found up to now, their Epidemiological Utilization and Stability]** *Zent. f. Bakt.* I. Abt. Orig. 1961, v. 182, No. 2, 191–200.

A survey of bacterophage typing of *Shigella sonnei* dysentery strains in Berlin and the surrounding district in the years 1955–60 is presented. The method of Hammarström was adopted and his phage preparations were used.

In view of the ever-present possibility of contamination of the *Sh. sonnei* cultures by other faecal bacteria and the possibility of modification of reactions by such strains if susceptible to the phage preparations used, a collection of 1,106 strains of other bacteria isolated from stools were investigated as well as 7,931 *Sh. sonnei* strains. The outcome has been to reveal 15 well-defined patterns of phage sensitivity among the *Sh. sonnei* strains—"lysotypes". In addition there were 206 (2·6%) which could not be typed. The control series included 569 salmonellae, 36 shigellae other than *Sh. sonnei*, 16 of the Arizona-Ballerup-Bethesda group, 409 *Escherichia coli*, 13 *Proteus* and 63 strains of bacillus.

Among the salmonellae there were 160 strains reacting with the test dilutions of the phage preparations used: among the Flexner strains 26 and among the escherichiae 11. Overall, therefore, 18%.

More than 6,000 of the *Sh. sonnei* strains came under five lysotypes. The constancy of the type in large epidemic outbreaks, in repeated isolations from the same patient and in small outbreaks in closed institutions all indicate type stability *in vivo* although from year to year the type which is most active will vary. A repetition of type determination on 1,732 strains kept in subculture for periods up to several years showed 94% of unchanged and 6% of modified type.

It is pointed out in this connexion that if subcultures are made at considerable intervals of time and are not made from tube to tube but with intervening plating and avoidance of colonies of unusual appearance, the likelihood of change of bacteriophage pattern is much lessened.

J. W. McLeod

HOFFMAN, H. & FRANK, M. E. **Form and Internal Structure of Cellular Aggregations in Early *Escherichia coli* Microcultures.** *J. General Microbiol.* 1961, July, v. 25, No. 3, 353–64, 3 text figs. & 38 figs. on 3 pls. [18 refs.]

Different microcultural methods were used in this study but the principal one involved the surface inoculation of a small thin film of agar on a coverslip. And the form of microculture studied in the greatest detail was the clonal microcolony.

The formation pattern of the microcolony at 37°C. appears to depend primarily on the fact that growth is in the direction of the longitudinal axis of the bacillus. If undisturbed the natural order would be a chain of bacteria, but further development depends on the availability of free space and generally results in palisading movements giving rise to parallel columns of bacteria approximating to each other. When palisading movements have established 3 or more columns, the exterior organisms continue to form new palisades, but the interior columns develop unbroken because of the pressure of the adjoining organisms. Centrally placed bacteria in interior columns are, however, forced up and over the original monolayer to form a second layer. As the process continues the typical convexity of a macrocolony gradually evolves. The interplay of movements and pressure regularly leads to a circular colony regardless of the early microcultural configuration.

At 44°C. palisading may not be a factor in the aggregation of the bacteria and close packing does not occur, but the formations will, nevertheless, eventually also become circular in spite of the fact that the organisms may appear to be arranged in a very irregular manner.

H. J. Bensted

MORRISON, R. B. **The Effect of Temperature and Chloramphenicol on the Development of Flagella and Motility in a Strain of *Escherichia coli*.** *J. Path. & Bact.* 1961, July, v. 82, No. 1, 189–92, 4 figs. on pl.

A strain of *Escherichia coli* after prolonged growth at 37°C. had lost its flagella. When a "dense" (4×10^9 per ml.) suspension in broth was kept at 20°C. about one-third of the cells grew flagella and were motile after 1

day. When the broth suspension contained 100 μgm. per ml. chloramphenicol, the viable count remained almost constant for 14 days instead of falling as in the antibiotic-free suspension (a paradoxical effect which is not discussed) and motility again developed, but "much more slowly". It is thought remarkable that an antibiotic which interferes with protein synthesis should fail to prevent the growth of flagella, but the author suggests that these may have been pre-formed in basal granules.
L. P. Garrod

COHEN, Flossie, PAGE, R. H. & STULBERG, C. S. **Immunofluorescence in Diagnostic Bacteriology. III. The Identification of Enteropathogenic *E. coli* Serotypes in Fecal Smears.** *Amer. J. Dis. Children.* 1961, July, v. 102, No. 1, 82–90, 4 figs. [12 refs.]

[There have been several papers during the last year or so dealing with the application of the fluorescent antibody technique for the identification of enteropathogenic *Escherichia coli* in faecal smears, and most of them are very similar. The present article is substantially the same as that by NELSON and WHITAKER (see this *Bulletin*, 1961, v. 36, 491) who appear to have some association with the authors of the paper under review.]

The results reported here are from specimens representative of sporadic infantile diarrhoea covering the 6 commoner serotypes of enteropathogenic *E. coli*, and although within the limits of the study the results appear to be satisfactory the authors do not make extravagant claims. They did not rely on faecal smears only but supplemented these with smears made from broth cultures; they assessed the combined results against serotype isolations by conventional bacteriological procedures and found there was about 87% agreement. Non-specific fluorescent staining is considered in relation to shared antigens by otherwise unrelated members of the Enterobacteriaceae; but the brilliant non-specific fluorescent staining of normal tissue fragments, necessitating elaborate adsorption procedures in many of the applications of the fluorescent antibody technique, does not appear, from the published accounts related to the enteropathogenic *E. coli*, to be a serious complication. The authors do, however, emphasize that the application of the fluorescent antibody technique to the study of enteropathogenic *E. coli* infections of the new-born is in fact a presumptive test for the presence of certain defined members of the group in the stool of the infant. Confirmatory bacteriological and serological procedures are essential. [For parts I and II, see this *Bulletin*, 1961, v. 36, 1052.] *H. J. Bensted.*

HAMON, Y., with the technical collaboration of Yvonne PÉRON. Colicines et lysotypie. **[Colicines and Phage Typing]** *Zent. f. Bakt.* I. Abt. Orig. 1961, v. 181, No. 4, 456–68, 2 figs. [10 refs.]

141 pathogenic strains of *Escherichia coli* isolated from children with gastro-enteritis in Germany were classified serologically, by phage type, by the type of colicine they produced and also by their sensitivity pattern towards 14 different colicines. Some strains of the same phage type which synthesized the same colicine nevertheless differed in colicine sensitivity. However, strains isolated from each epidemiological focus generally produced the same colicine and displayed the same type of colicine sensitivity. *Janice Taverne*

MIYAMA, A., OZAKI, M. & AMANO, T. **Double Colicinogenicity of *Escherichia coli* K235.** *Biken's J.* Osaka. 1961, Mar., v. 4, No. 1, 1–11, 4 figs. (3 on 3 pls.) [11 refs.]

KILGORE, W. W. & GREENBERG, J. **Filament Formation and Resistance to 1-Methyl-3-Nitro-1-Nitrosoguanidine and other Radiomimetic Compounds in *Escherichia coli*.** *J. Bacteriology.* 1961, Feb., v. 81, No. 2, 258–66, 3 figs. [18 refs.]

SAWADA, F. & SUZUKI, K. **Recovery of *Escherichia coli* irradiated with Ultraviolet Light.** *J. Bacteriology.* 1961, Feb., v. 81, No. 2, 288–97, 8 figs. [12 refs.]

SAHAB, K. ***Escherichia coli* A Antigen.** *J. Bacteriology.* 1961, Mar., v. 81, No. 3, 346–52. [12 refs.]

BACON, D. F. & TREFFERS, H. P. **Spontaneous and Mutator-Induced Reversions of an *Escherichia coli* Auxotroph. I. Prototrophic Types and their Growth Characteristics.** *J. Bacteriology.* 1961, May, v. 81, No. 5, 786–93, 4 figs. [27 refs.] **II. Acetylornithinase Activity associated with the Different Revertant Types.** *Ibid.*, July, v. 82, No. 1, 48–53, 3 figs.

LESTER, G. & YANOFSKY, C. **Influence of 3-Methylanthranilic and Anthranilic Acids on the Formation of Tryptophan Synthetase in *Escherichia coli*.** *J. Bacteriology.* 1961, Jan., v. 81, No. 1, 81–90, 1 fig. [19 refs.]

NOVICK, R. P. & MAAS, W. K. **Control by Endogenously Synthesized Arginine of the Formation of Ornithine Transcarbamylase in *Escherichia coli*.** *J. Bacteriology.* 1961, Feb., v. 81, No. 2, 236–40, 3 figs. [10 refs.]

ECHOLS, H., GAREN, A., GAREN, S. & TORRIANI, A. **Genetic Control of Repression of Alkaline Phosphatase in *E. coli*.** *J. Molecular Biol.* London. 1961, Aug., v. 3, No. 4, 425–38, 6 figs. [17 refs.]

PAEGE, L. M. & GIBBS, M. **Anaerobic Dissimilation of Glucose-C^{14} by *Escherichia coli*.** *J. Bacteriology.* 1961, Jan., v. 81, No. 1, 107–10. [18 refs.]

Szynkiewicz, Z. M., Sable, H. Z. & Pflueger, E. M. **Biosynthesis of Pentoses in *Escherichia coli*. Factors involved in Selection of Biosynthetic Pathways.** *J. Bacteriology.* 1961, June, v. 81, No. 6, 837–44. [19 refs.]

Wright, E. M., Sable, H. Z. & Bailey, Joy L. **Biosynthesis of Pentose in *Escherichia coli*. Synthesis of Deoxyribose in Cells infected with Bacteriophage.** *J. Bacteriology.* 1961, June, v. 81, No. 6, 845–51. [24 refs.]

Englesberg, E. **Enzymatic Characterization of 17 L-Arabinose Negative Mutants of *Escherichia coli*.** *J. Bacteriology.* 1961, June, v. 81, No. 6, 996–1006, 1 fig. [28 refs.]

Rhuland, L. E. & Hamilton, R. D. **The Functional Pathway of Lysine Biosynthesis in *Escherichia coli*.** *Biochim. et Biophys. Acta.* 1961, Aug. 19, v. 51, No. 3, 525–8, 1 fig. [13 refs.]

Ennis, H. L. & Gorini, L. **Control of Arginine Biosynthesis in Strains of *Escherichia coli* not Repressible by Arginine.** *J. Molecular Biol.* London. 1961, Aug., v. 3, No. 4, 439–46, 1 fig. [13 refs.]

Pichinoty, F. & D'Ornano, Liliane. **Inhibition by Oxygen of Biosynthesis and Activity of Nitrate-Reductase in *Aerobacter aerogenes*.** *Nature.* 1961, Aug. 26, v. 191, 879–81, 2 figs.

Wood, W. A., McDonough, M. J. & Jacobs, L. B. **Ribitol and D-Arabitol Utilization by *Aerobacter aerogenes*.** *J. Biol. Chem.* 1961, Aug., v. 236, No. 8, 2190–95, 5 figs. [28 refs.]

Lautrop, H. ***Bacterium anitratum* transferred to the Genus *Cytophaga*.** *Internat. Bull. Bact. Nomencl. & Taxon.* 1961, July 15, v. 11, No. 3, 107–8.

Bacterium anitratum [an organism commonly isolated from urine and occasionally from pus] has been found difficult to classify and placed, by various authors, in at least 5 different bacterial families. Lautrop now reports that 10 of 15 strains showed a gliding type of motility when grown on thin layers of agar of a poor nutritional quality. The movement is described as "slow, hesitating, and intermittent as in other myxobacteria". Fruiting bodies were not found, and the organism was, therefore, assigned to the genus *Cytophaga* as *Cytophaga anitrata*.

A few strains of the organism originally designated *Moraxella lwoffii* were examined and these, too, were found to show a gliding motility. Lautrop is not sure that both these closely related organisms justify the establishment of two species, but if they do *M. lwoffii* would become *Cytophaga lwoffii*.

[Lautrop does not mention that if both these organisms are regarded as one species, priority will make the correct name for the combined species *C. lwoffii*, with *C. anitrata* as a synonym.] *S. T. Cowan*

Guillaume, J., Osteux, R. & Wattel, F. Étude métabolique de souches de *Proteus mirabilis* auréomycino-résistantes cultivées sur milieu complexe. [**Metabolic Study of Chlortetracycline-Resistant Strains of *Proteus mirabilis* cultivated in a complex Medium**] *C.R. Soc. Biol.* 1961, v. 155, No. 1, 81–4.

These authors from Lille have compared the metabolic activities of a strain of *Proteus mirabilis* sensitive to chlortetracycline with those of a resistant variant, and claim to have shown that the difference between them is the capacity of the resistant variant to metabolize glucose by some process departing from the Krebs cycle. Evidence for this is that (1) in the presence of intermediates, fluoracetate fails to inhibit the resistant variant, and (2) the resistant variant fails to form acetate from glucose in the presence of the antibiotic. *L. P. Garrod*

Altenbern, R. A. **Critical Factors influencing Growth of L Forms of *Proteus mirabilis*.** *J. Bacteriology.* 1961, Apr., v. 81, No. 4, 586–94, 3 figs.

Morgan, W. J. B. **The Use of the Thionin Blue Sensitivity Test in the Examination of *Brucella*.** *J. General Microbiol.* 1961, May, v. 25, No. 1, 135–9. [10 refs.]

Standard strains of *Brucella abortus, Br. melitensis* and *Br. suis* were found to grow in the presence of thionin-blue in concentrations of up to 1/500,000. When 171 cultures of brucellae, mainly recently isolated in Great Britain from milk and foetal material, were examined for sensitivity to thionin-blue in addition to the usual dyes, and for agglutination with monospecific sera, it was found that typical strains of the three organisms all grew in the presence of 1/500,000 thionin-blue, but that a number of strains of *Br. abortus*, divisible into 3 groups, were sensitive to this dye. The largest group, comprising 15·2% of the total examined, belonged to type II (Wilson), which is known to be sensitive to most dyes. A second group, 4·7% of total, had all the biochemical reactions of the vaccine strain 19 *Br. abortus*, and the third group, 4·1% of total, differed from type II (Wilson) in that the organisms grew in the presence of basic fuchsin and differed from strain 19 in requiring additional CO_2 for growth.

Of particular interest were the cultures resembling strain 19 since they were isolated both from foetal material and from milk and it is said that strain 19 does not appear in the milk of cows when this vaccine strain of *Br. abortus* is inoculated subcutaneously. Some of the strains of these cultures resembling strain 19 were examined in parallel with the reference strain for virulence in guineapigs and found to have the same low virulence. By present methods they could not be distinguished from the true *Br. abortus* vaccine strain 19 apart from the isolation history. *H. J. Bensted*

Lukás, B. & Vlasák, Z. Primokultivace *Pasteurella tularensis* ze spojivkového vaku člověka na nové jednoduché tuhé a tekuté půde. [**Primary Isolation of *Brucella tularensis* from the Human Conjunctival Sac on New Solid and Liquid Media**] *Československ. Epidemiol., Mikrobiol., Imunol.* Prague. 1961, v. 10, No. 2, 121–3. [18 refs.] English summary (4 lines).

The authors describe solid and liquid media which can be used for the direct isolation of *Br. tularensis* from human pathological material. The solid medium consists of 0·4% sodium thioglycollate, 1% glucose, 1% of a Czechoslovak brand of peptone and 10% defibrinated rabbit blood to each 5 cc. A laboratory infection is described in which *Br. tularensis* gained access to the conjunctiva and led to the development of the oculoglandular form of tularaemia. Inoculation of conjunctival scrapings on the new media led to growth of *Br. tularensis* within 48 hours. *D. J. Bauer*

Huziwara, T., Watanabe, Y. & Hyôdô, S. Phagocytose *in vitro* de *Past. tularensis* par les macrophages de cobaye. Relation entre phagocytose et virulence de bactérie. [**Phagocytosis *in vitro* of *Brucella tularensis* by Guineapigs Macrophages. Relation between Phagocytoses and Virulence**] *C.R. Soc. Biol.* 1960, v. 154, No. 12, 2407–10. [10 refs.]

The multiplication of bacteria within various mammalian cells in tissue culture experiments has been studied by a number of workers. The present paper is concerned with the difference in the phagocytosis by guineapig macrophages of virulent and avirulent *Brucella tularensis* as seen in *in vitro* cultures of these cells obtained from the peritoneal fluid of the guineapig and grown in a medium containing fresh guineapig serum in Hanks' balanced salt solution. Virulent cultures of *Br. tularensis* were found to be more readily, and more abundantly, phagocytosed than avirulent cultures. Moreover the proportion of viable organisms recovered from the phagocytosed virulent strain of *Br. tularensis* was very much greater than from the avirulent; indeed after 12 hours' incubation all the avirulent organisms appeared to be dead.

[Independently of the work described in this paper, Merriott *et al.* (this *Bulletin*, 1961, v. 36, 1189) conducted some rather more elegant experiments with different strains of *Br. tularensis* of measured virulence for rabbits, mice and guineapigs, using cell cultures of mouse L fibroblasts, bovine kidney cells and human amnion cells. As in similar studies with *Br. abortus*, they found that highly virulent and moderately virulent strains of *Br. tularensis* were ingested by, and multiplied within, the cells of the tissue culture employed, but that avirulent strains, even when heavy doses of the organisms were added to the cell cultures, failed to show any evidence of intracellular growth.] *H. J. Bensted*

McElree, Helen & Downs, Cora M. **The Phagocytosis of *Pasteurella tularensis* by Rat Mononuclear Cells as influenced by Normal Serums and Various Irritants.** *J. Infect. Dis.* 1961, July–Aug., v. 109, No. 1, 98–106, 4 figs. [23 refs.]

Marchette, N. J. & Nicholes, P. S. **Virulence and Citrulline Ureidase Activity of *Pasteurella tularensis*.** *J. Bacteriology.* 1961, July, v. 82, No. 1, 26–32, 2 figs. [22 refs.]

Mollaret, H. H. A propos de l'action *in vivo* de l'auréomycine sur *Pasteurella pseudotuberculosis* (bacille de Malassez et Vignal). [**On the Action *in vivo* of Aureomycin on *Pasteurella pseudotuberculosis***] *C.R. Soc. Biol.* 1961, v. 155, No. 1, 31–3. [18 refs.]

Pasteurella pseudotuberculosis is said to be consistently sensitive to chlortetracycline *in vitro*, but according to some workers the administration of this antibiotic to animals infected with the organism actually accelerates death. This paper reports somewhat similar observations. Guineapigs were infected orally with *P. pseudotuberculosis*: most of them died, and the survivors were given 40 mgm. chlortetracycline orally daily for 5 days after an interval of 2 months. Some of these then developed fatal haemorrhagic enteritis with the organism in the faeces (previously absent) but without the other visceral lesions of the disease. Some episodes involving pigs and a dog are referred to which may also illustrate the reactivation of this infection in this way. The author wonders whether the "disequilibrium" of the intestinal flora caused by chlortetracycline may be a factor. [He does not mention that tetracyclines, like penicillin, are exceptionally toxic to guineapigs, although to not quite the same degree as penicillin. Diarrhoea is a feature of this toxic state.] *L. J. Garrod*

Jackson, S. & Morris, B. C. **Enhancement of Growth of *Pasteurella pestis* and other Bacteria in Serum by the Addition of Iron.** *Brit. J. Exper. Path.* 1961, Aug., v. 42, No. 4, 363–8.

[An abstract of this paper appeared in the *Tropical Diseases Bulletin*, 1961, v. 58, 1345.]

Chen, T. H., Foster, L. E. & Meyer, K. F. **Experimental Comparison of the Immunogenicity of Antigens in the Residue of Ultrasonated Avirulent *Pasteurella pestis* with a Vaccine prepared with Killed Virulent Whole Organisms.** *J. Immunology.* 1961, July, v. 87, No. 1, 64–71, 1 fig. [14 refs.]

[An abstract of this paper appeared in the *Tropical Diseases Bulletin*, 1961, v. 58, 1347.]

Levi, M. I., Chekomasova, A. V. & Vasil'ev, N. V. **A Study of the Possibility of increasing the Viability and Antigenicity of Live Avirulent Plague Vaccine—Passage of Vaccine Strain 1 in White Mice.** *J. Microbiol., Epidemiol. & Immunobiol.* London. 1960, v. 31, No. 8, 1512–20. [Translated from Russian.]

[An abstract of this paper appeared in the *Tropical Diseases Bulletin*, 1961, v. 58, 1347.]

GILLISSEN, G. & SCHOLZ, H. G. Die Selektion von Milzbrandbazillen aus Flüssigkeiten mit starker Verunreinigung durch *E. coli*. [**The Selection of Anthrax Bacilli from Liquids grossly contaminated with *E. coli***] *Zent. f. Bakt.* I. Abt. Orig. 1961, v. 182, No. 2, 232–7.

Use is made of the facts that anthrax spores do not germinate on a synthetic medium, the details of which are given, and that in the spored condition they readily resist a concentration of 100 μgm. polymyxin per ml.

Mixed cultures containing *Escherichia coli, Staphylococcus albus*, and *Bacillus mesentericus*, if left in contact with the synthetic medium to which 0·01% polymyxin has been added, will yield subcultures on the usual nutrient media in which *Bacillus anthracis* will predominate.

Separation from *Bacillus subtilis* is not, however, readily effected by this method. *J. W. McLeod*

HORODNICEANU, Thea & SĂSĂRMAN, A., with the technical collaboration of Rodica CIULLEY. Recherches sur les pénicillinases bactériennes. Note III. Relations entre l'élaboration de la pénicillinase et la sensibilité à la pénicilline des souches de *B. anthracis*. [**Study of Bacterial Penicillinases. III. Relationships between Penicillinase Production and Susceptibility to Penicillin in *B. anthracis* Strains**] *Arch. Roumaines Path. Expér. et Microbiol.* 1961, June, v. 20, No. 2, 257–62. [11 refs.]

These authors examined 115 strains of *Bacillus anthracis*, determining the amount of penicillinase formed by them, and the minimum inhibitory concentration of penicillin by "the dilution method" (size of inoculum not stated). This concentration varied from 0·001 to 0·06 (most often 0·015) unit per ml., and was unrelated to the amount of penicillinase formed, which varied from 6·25 to 1,600 units/ml. of culture (a definition of the unit referred to is given). It thus appears that the degree of susceptibility to penicillin, at least in this species, depends on some mechanism other than the formation of this enzyme. *L. P. Garrod*

BITTNER, J., ANTOHI, S. & VOINESCO, Viorica. Recherches "in vitro" concernant l'action des associations d'antibiotiques sur les anaérobies du genre *Clostridium* (communication préliminaire). [***In vitro* Investigations concerning the Action of Antibiotic Combinations on Anaerobes of the *Clostridium* Genus (Preliminary Communication)**] *Arch. Roumaines Path. Expér. et Microbiol.* 1961, June, v. 20, No. 2, 263–8.

These authors have followed a previous study of the action of single antibiotics on various species of *Clostridium* [this *Bulletin*, 1961, v. 36, 808] by testing the action of pairs on 7 of the more important pathogenic species. The 5 antibiotics of which every possible combination (10) was tested were penicillin, chlortetracycline, chloramphenicol, streptomycin and bacitracin, and 13 different total and relative quantities of each pair were tested, details of which are given for only one pair. The disc method was used, and a combination was considered synergic or antagonistic if the inhibition zone produced was at least 20% wider or narrower than that produced by the more active of the 2 antibiotics singly (each was also tested alone, and presumably with discs containing all the different amounts in the various combinations). Of the numerous results so obtained, 69·2% showed indifference, 25·3% synergy and 5·5% antagonism.

[The significance of results so obtained is questionable. Several "synergic" pairs included streptomycin, which has so low a degree of activity against organisms of this genus (GARROD, *ibid.*, 1959, v. 34, 495) that its choice for inclusion in such tests is surprising: there is no information about the quantities of it which were used.]

L. P. Garrod

ROWSON, K. E. K. **The Action of Tetanus Toxin in Frogs.** *J. General Microbiol.* 1961, June, v. 25, No. 2, 315–29, 3 figs. on pl. [31 refs.]

The relatively limited earlier work on the reaction of cold-blooded vertebrates to tetanus toxin is extended by experimental work on frogs. The chief conclusions reached are that below 15°C. the frog is immune to tetanus although this is not due to failure of absorption and distribution of toxin in the tissues since an animal receiving an adequate injection of toxin will remain symptomless if kept at a low temperature for many days only to die with characteristic tetanic symptoms on being exposed to temperature of 20–25°C. Localized tetanus is produced if the toxin is given intramuscularly to an animal already protected from generalized tetanus by injection of antitoxin to the dorsal lymph sac.

As in warm-blooded vertebrates the toxin is much more effective if given by the intracerebral route, but all attempts to demonstrate neutralization of tetanus toxin by suspensions of frog cerebral matter have failed although parallel observations with mouse brain showed neutralization of 90% of the toxin. *J. W. McLeod*

CRAIG, J. P. & MILES, A. A. **Some Properties of the Iota-Toxin of *Clostridium welchii*, including its Action on Capillary Permeability.** *J. Path. & Bact.* 1961, Apr., v. 81, No. 2, 481–93, 6 figs. [10 refs.]

In a strain of *Cl. welchii* type E it has been possible to demonstrate the presence of a toxin which increases capillary permeability in the guineapig. The method adopted is to make multiple dilutions of toxin which are injected intracutaneously along the animal's flank and 5 hours later to inject intravenously a 5% solution (in 0·425% saline) of the dye pontamine sky blue 6XB in the ratio of 1·2 ml./kgm. of body weight. Zones of "blueing" of variable diameter develop in the injected areas and the dilution producing an 8 mm. reaction is assumed to contain 1 blueing unit in 0·1 ml.

It was found that 38 such units correspond to the LD50 for a mouse and parallel titrations showed a close correspondence between iota toxin (mouse lethal effect) and the factor affecting capillary permeability. This

correspondence was borne out by titrations against a variety of antisera which were found to neutralize the 2 effects equally. The toxin is stable at low temperatures, readily destroyed by temperatures above 50°C. and appears in cultures as a protoxin rapidly activated by proteolytic enzymes present in the cultures. It is destroyed readily at *p*H levels outside the range 4–9. The guineapig test for increased capillary permeability can therefore be used as a rapid and economical test in the production of iota toxin and in the titration of its antitoxin. *J. W. McLeod*

Olaru, A., Bittner, Z., Teodorescu, G. & Fychiu, S. **Study of Toxin Formation by *Clostridium perfringens* in a Medium produced by Hydrolysis of Casein and Fishbone Meal by Protease from the Fungus *Aspergillus terricola*.** *J. Microbiol., Epidemiol. & Immunobiol.* London. 1960, v. 31, No. 10, 1880–85, 6 figs. [Translated from Russian.]

Stephen, J. **The Isolation of the α-Toxin of *Clostridium welchii* Type A by Zone Electrophoresis in Vertical Columns.** *Biochem. J.* 1961, Sept., v. 80, No. 3, 578–84, 4 figs. & 1 pl. [33 refs.]

Jansen, B. C. **The Beta Toxin of *Clostridium welchii* Type B, Wilsdon, in relation to the Production of a Vaccine against Lamb Dysentery.** *Onderstepoort J. Vet. Res.* 1961, May, v. 28, No. 4, 495–549, 9 figs. [Numerous refs.]

Vaneseltine, W. P. & Staples, Sarah A. **Nutritional Requirements of Leptospirae. I. Studies on Oleic Acid as a Growth Factor for a Strain of *Leptospira pomona*.** *J. Infect. Dis.* 1961, May–June, v. 108, No. 3, 262–9, 3 figs. [11 refs.]

Pathogenic leptospires will grow in artificial media if these contain whole blood or serum. Results of earlier work suggested that one of the growth factors may be an unsaturated fatty acid, alcohol-soluble, carried on or bound by serum albumin which may itself be needed as a detoxifier for the fatty acids.

The authors used *Leptospira pomona* (strain T-262) to study the effects of oleic acid as a growth factor. Liquid and semi-solid media were used; the basal medium, a modification of Greene's contained salts, amino acids, vitamins, purines and pyrimidines. Growth of leptospires was measured either by counts or turbidimetrically [full details are given].

Chloroform extraction of serum reduced its growth-promoting activity: this suggests that a necessary lipid material was removed. The addition of oleic acid or Tween 80 partially restored this activity but high concentrations of these substances appeared to be toxic. Various concentrations of Tween 80 and oleic acid were overlaid on top of semi-solid serum-free medium: narrow bands developed in the medium at depths depending on the concentration of the overlay. Leptospires from above the bands were non-motile, those from within the bands and below them were motile: this suggests that a level occurs where the leptospires utilise the oleate at the same rate as it diffuses down. The visible bands indicate levels of maximum growth of the leptospires.

Attempts to subculture the organism in serum-free medium by using sections from the bands of growth as inoculum were unsuccessful. Moreover, the use of washed leptospires failed to produce growth bands in semi-solid medium. These findings suggest that other, unidentified, factors present in serum are also needed. *L. H. Turner*

Trainer, D. O., Jr., Karstad, L. & Hanson, R. P. **Experimental Leptospirosis in White-Tailed Deer.** *J. Infect. Dis.* 1961, May–June, v. 108, No. 3, 278–86, 3 figs. [27 refs.]

Serological evidence of leptospirosis in deer in the U.S.A. was first reported in 1956; further surveys throughout the deer range of the country have established the prevalence of reactors to *Leptospira pomona*. Because of the close contact which often exists between deer and domestic cattle, these findings aroused special interest. The authors therefore investigated several aspects of this situation: the significance of the serological reactions, the pathogenicity of leptospires for deer, and the role of deer in the epizootiology of leptospirosis.

Serologically negative white-tailed deer (*Odocoileus virginianus*) were caught wild as fawns aged 2 weeks or less and were isolated in captivity until used experimentally at ages ranging from 6 weeks to 2 years. *Leptospira pomona* (LT 407), isolated in Georgia, was used as inoculum [2 ml. containing about 10^9 organisms per ml.]. Intradermal (near the mouth) and intraperitoneal routes of inoculation gave similar results and the latter was adopted as a routine.

10 non-pregnant deer were inoculated. Leptospires were isolated from the blood on day 1 in 2 deer, on day 2 in 5, on day 3 in 8, and on day 4 in 1. 2 animals were negative throughout but both yielded positive cultures from urine on day 15. 5 other animals studied gave positive urine cultures between day 15 and day 25 (negative on day 30). Leptospires were present in kidney tissues of 4 deer at days 7, 15, 25 and 30 but were not isolated from animals killed at 35 and 143 days after inoculation. Agglutinating antibodies in some appeared on day 5, reached a peak (1 in 100,000) between days 15 and 35, usually began to decline at around day 50, and after day 100 the titre dropped rapidly.

No clinical evidence of leptospirosis developed in any of these 10 deer; nor were there any abnormal haematological findings. Scattered white foci (1–6 mm. diameter) in the kidney cortex were the only gross pathological lesions seen: these only occurred in fawns. Histopathological findings resembled those seen in infected cattle.

4 of 5 pregnant does which were inoculated aborted at 12–25 days after inoculation: the estimated ages of the foetuses were 150–180 days. Leptospires were isolated from the liver, blood and kidney of the foetuses. One doe did not abort: she had leptospiraemia after inoculation and an agglutinin titre of 1 in 10,000 at the

time of parturition. Her 2 fawns had antibody titres of 1 in 10,000 at the second day after birth: one was killed and attempts to isolate leptospires were unsuccessful; the other lived and was sero-negative at 1 month (when the doe's titre was still 1 in 10,000).

Attempts to infect deer by isolating them with a known urinary shedder of leptospires were unsuccessful.

L. H. Turner

STURDZA, Nina, ELIAN, M. & TULPAN, Gertruda. **Diagnosis of Human Leptospirosis by the Complement Fixation Test with a Single Antigen. Note I.** *Arch. Roumaines Path. Expér. et Microbiol.* 1960, Dec., v. 19, No. 4, 571–82, 2 graphs. [13 refs.]

In an effort to produce a diagnostic test for leptospirosis which could be used in any laboratory accustomed to performing complement-fixation tests (CFT), the authors investigated *Leptospira biflexa* (Patoc strain) as a suitable single antigen. *L. biflexa* (Patoc) was earlier found [this *Bulletin*, 1959, v. 34, 334] to agglutinate with human sera which agglutinated several unrelated serotypes of *Leptospira*.

The antigen was prepared by taking cultures (in Korthof's medium) 10–12 days old and centrifuging them at 4,000 r.p.m. for 1½ hours; the sediment was resuspended in physiological saline to 1/20 the original volume, and merthiolate was added to a final concentration of 1/10,000. Stored at 4°C., this antigen was stable for 6 months.

BENGTSON'S technique was followed for the CFT [see GAEHTGENS, *Klin. Woch.*, 1933, v. 12, 697]; serial 2-fold dilutions of inactivated serum (from 1 in 4), 4 units of antigen, and 2 units of complement were used; the haemolytic system was added after 1 hour of incubation at 37°C.; and tests were read after 2 and 18 hours' incubation at room temperature. A minimum of +++ fixation was regarded as significantly positive.

The antigen was used in testing various sera:—

(1) *Immune rabbit sera* prepared against the following serotypes (living suspensions of which were used in comparative agglutination [ALT] tests): *poi, canicola, ballum, autumnalis, australis, pomona, grippotyphosa, hebdomadis, sejroe, bataviae, mitis.* All gave CFT titres of 1 in 64 to 1 in 256. The *biflexa* serum titred 1 in 4,096 but the *icterohaemorrhagiae* serum titred only 1 in 8.

(2) *Human sera*, positive by ALT, which had been stored at +4°C. for 1–4 years: 15 were positive by ALT (1 in 400–1 in 6,000) and CFT (1 in 32–1 in 64), 10 were negative by CFT (ALT titres, 1 in 100–1 in 1,600), and 1 was negative by both tests. Storage of the sera may have affected these results.

(3) *Horse sera* (16 out of 20 positive by ALT) and *hog sera* (25 of 26 positive by ALT) were all (46) negative by CFT.

(4) *Recently collected human sera* obtained from patients with various conditions were all negative by ALT and CFT: pyrexia of unknown origin, 50; pregnancies, 15; epidemic hepatitis, 35; syphilis (Wassermann tests positive), 32; malaria, 4.

(5) *Recently collected human sera* of 2 categories were also examined. First, serial specimens were obtained from 79 patients with clinical leptospirosis: rising titres, ALT and CFT, confirmed the diagnosis. The peak titres were reached in the 3rd week (CFT) and 5th week (ALT) of illness. The seropositivity rates (%), ALT/CFT, were—week I, 38/55; II, 79/90; III, 100/98; IV, 100/100; V, 100/100; VI, 90/70. There was 79% agreement between ALT and CFT among the total of these examinations. Secondly, single specimens were obtained from 44 patients in whom the serological findings were suggestive of leptospirosis: in this group, too, both tests were positive in the majority of patients, but the CFT alone was positive in 4 of 19 sera obtained in the first week.

The authors stress the need for further large-scale comparative tests to determine the polyvalence of their antigen.

L. H. Turner

FÜZI, M. & CSÓKA, Rózsa. Über die systematische Stellung der *Leptospira semaranga* und *Leptospira andamani* A. [**The Systematic Position of *Leptospira semaranga* and *Leptospira andamani* A**] *Zent. f. Bakt.* I. Abt. Orig. 1961, v. 182, No. 4, 494–500. [20 refs.]

The English summary appended to the paper is as follows:—

"The standard strains of the serotypes L. semaranga and L. andamani A, which are registered as pathogenic have no virulence for laboratory animals and they display the biologic characteristics of water leptospira. There are no closer serologic relations to the serotypes of the parasitic group, however, there is an antigen relationship to water leptospira. According to these results it could be recommended to classify both strains into the Biflexa group."

LINSCOTT, W. D.; BOAK, Ruth A. **Immune-Adherence with *Leptospira* Antigens. I. Studies on the Immune-Adherence Phenomenon** [LINSCOTT & BOAK]. *J. Immunology*. 1961, May, v. 86, No. 5, 471–9, 2 figs. [19 refs.] **II. Studies on Hyperimmune, Convalescent and Normal Sera** [LINSCOTT]. *Ibid.*, 480–88, 1 fig. [24 refs.]

I. NELSON used the term "immune-adherence" (I-A) to describe the phenomenon of adhesion of red blood cells to *Treponema pallidum* [this *Bulletin*, 1953, v. 28, 535] and he concluded that 3 steps occurred in this reaction: sensitization of the organisms by antibody, binding of complement to the sensitized organism-antibody complex and adhesion of this antigen-antibody-complement complex to the erythrocytes of primates.

The authors adapted Nelson's procedure for use with *Leptospira* antigens and employed *L. canicola* (Utrecht IV) living and merthiolated, 2 immune rabbit sera, human erythrocytes (of any type), and human or guineapig complement. 3 controls were used of which the spontaneous adherence (SA) control was the most

important. Tests were read by counting unattached leptospires after centrifuging the tubes and results were calculated from the formula:

$$\frac{\text{count in SA control—count in test tube}}{\text{count in SA control}} \times 100 = \% \text{ adherence}$$

50% adherence was adopted as significant and titres were determined by interpolation if necessary.

The quantitative I-A test was reproducible; live and merthiolated antigens reacted similarly; the sensitivity of the test could be varied by altering the concentration of leptospires. The I-A bond between erythrocyte and sensitized antigen particles was quite firm but could be disrupted by vigorous agitation; complete re-adherence occurred after four successive disruption—re-adherence cycles but thereafter weakened.

The % adherence obtained with various conditions of antigen sensitization and different testing conditions is reported.

Substances, resembling "natural" antibodies, which are present in complement and active in I-A tests against several serotypes often caused false positive reactions: the activity of these substances can be "diluted out" by using complement at 1 in 400.

The I-A reaction was sufficiently sensitive for antibodies to be detected within 40 hours of the initial dose of homologous suspensions used in immunizing a rabbit.

II. Immune-adherence (I-A) and microscopic agglutination (M-A) tests with living *Leptospira* antigens were compared in parallel against 10 hyperimmune rabbit sera (10 serotypes) and convalescent sera (human and domestic animal); 10 antigens, homologous with the several rabbit sera, were used.

Sera obtained from the rabbits before immunization were all negative in the M-A test and in the I-A test they reacted only with *L. biflexa*. Comparison of the results of the tests with homologous and heterologous antisera showed that the I-A test was more sensitive; but there was general agreement both qualitative and quantitative. The reactivity of the I-A test with *L. biflexa* did not increase when the rabbits were immunized with any of the other 9 serotypes used; nor did immunization with *L. biflexa* result in detectable antibodies against the other serotypes.

Tests with the convalescent sera revealed a less close correlation between the 2 tests than that obtained with the immune sera: I-A titres were 3 to 200 times the M-A titres, but this was probably due to the necessity to use dilute complement in the I-A test. Under optimum conditions I-A titres would probably be about 100 times as high as the corresponding M-A titres.

"Natural" serum antibodies, usually present only in low titre, were shown to be specific for certain strains and in some cases discriminated between strains of the same serotype. Sera from different guineapigs varied considerably in their activity against any particular serotype. None of 5 guineapig sera, which reacted with one or more test antigens, reacted with these antigens in the M-A test even at a final dilution of only 1 in 10. The variation, among individual animals, in patterns of natural adherence activity was less marked with individuals from an in-bred line than with those from a random-bred population.

The "natural" antibodies were shown to be heat-stable but were not removed by absorption with inulin or amylose. In a brief investigation, normal human sera (heat-inactivated) showed marked but variable I-A activity against a wide range of leptospires; rabbit sera reacted only with *L. biflexa*. The occurrence of "natural" antibodies may be due to various substances and micro-organisms, present in the environment, having similar antigenic groupings.

The great sensitivity of the I-A test may be of use in early detection of infection, or of the persistence of antibody long after exposure to antigen, and in the detection of minimal amounts of antibody as, for example, might arise from the presence of leptospires in an inoculum. *L. H. Turner*

HAMPP, E. G. & MERGENHAGEN, S. E. **Experimental Infections with Oral Spirochetes.** *J. Infect. Dis.* 1961, July–Aug., v. 109, No. 1, 43–61, 24 figs. [38 refs.]

BACTERIOPHAGES

LEVIN, A. P. & BURTON, K. **Inhibition of Enzyme Formation following Infection of *Escherichia coli* with Phage T2r+.** *J. General Microbiol.* 1961, June, v. 25, No. 2, 307–14, 4 figs. [31 refs.]

After infection with a lytic phage or its ghosts, *Escherichia coli* cells do not synthesize some inducible enzymes (*e g.* BENZER, *Biochim. et Biophys. Acta*, 1953, v. 11, 383). The same is now found to be true of some enzymes which, in certain conditions, are DNA precursors.

A strain of *E. coli* B which did not synthesize aspartate carbamyl transferase (ureidosuccinic synthetase) or dihydroorotic dehydrogenase when uracil was present was suspended in a medium lacking uracil and then mixed with either T2r+ phage or its ghosts. The synthesis of both enzymes was inhibited. The synthesis of a third enzyme, alkaline phosphatase, was not affected by uracil but was inhibited either by the addition of inorganic phosphate to the medium or by infection with the phage or its ghosts. It is known that infection with T2 is followed immediately by the breakdown of host DNA and, as one possible explanation of their results, the authors suggest that enzymes may not be synthesized in the cell unless bacterial DNA is intact. *Janice Taverne*

PRATT, D., STENT, G. S. & HARRIMAN, P. D. **Stabilization to ^{32}P Decay and Onset of DNA Replication of T4 Bacteriophage.** *J. Molecular Biol.* London. 1961, Aug., v. 3, No. 4, 409–24, 5 figs. [43 refs.]

JINKS, J. L. **Internal Suppressors of the *h*III and *tu*45 Mutants of Bacteriophage T4.** *Heredity.* 1961, Aug., v. 16, Pt. 3, 241–54, 1 fig.

CAMPBELL, A. **Sensitive Mutants of Bacteriophage λ.** *Virology.* New York. 1961, May, v. 14, No. 1, 22–32, 4 figs. [19 refs.]

130 mutants of λ phage obtained as survivors of UV restoration experiments gave rise to small plaques on *Escherichia coli* K12 sub-strain C600 but did not grow on sub-strain W3350. As a result of complementation tests, the mutants could be placed in one of 18 classes so that a mutant of 1 class when mixed with 1 of another class, but not with 1 of its own class, gave rise to massive lysis on plating on strain W3350. The mutants were mapped by crossing with galactose-transducing phages. It was found that for each class the mutations had occurred close together on the chromosome, probably in the same locus. [Incidentally, this work indicates that the λ chromosome is topologically linear over a region containing at least 8 loci, thus extending BENZER's work (*Proc. Nat. Acad. Sci. U.S.*, 1959, v. 45, 1607) which showed it to be linear within the locus.] As one complementation class of mutants did not contain the lytic enzyme (endolysin) described by JACOB *et al.* [this *Bulletin*, 1958, v. 33, 525], it is presumed that this same locus also controls the production of endolysin. 19 other mutants were found to be heat-sensitive, failing to plate on C600 at 43°C., and these appeared to have resulted from mutations in the same general region of the chromosome. 2 mutants isolated were sensitive to extremes of *p*H.

The author [mainly on grounds of "sectarian prejudice"] favours the hypothesis that the mutants contain an abnormal protein which is sensitive to suppression when growing in most bacterial strains. In strain C600, however, the suppressor gene has mutated and the phage mutants (named *sus* for susceptible to suppression) can grow. The mutants form defective lysogens in strain W3350, some of which can be induced by UV light, and the author points out that if the work had been done with W3350 alone the mutants would have been classified as true defectives. It is possible that other defective phages described may in fact only be susceptible to suppression.

Janice Taverne

WEIGLE, J. **Densities of Transducing Lambda Bacteriophages.** *J. Molecular Biol.* London. 1961, Aug., v. 3, No. 4, 393–8, 1 fig.

KELLENBERGER, G., ZICHICHI, M. L. & WEIGLE, J. **A Mutation affecting the DNA Content of Bacteriophage Lambda and its Lysogenizing Properties.** *J. Molecular Biol.* London. 1961, Aug., v. 3, No. 4, 399–408, 4 figs. & 1 pl. [13 refs.]

MEYNELL, Elinor W. **A Phage, $\phi\chi$, which attacks Motile Bacteria.** *J. General Microbiol.* 1961, June, v. 25, No. 2, 253–90, 1 text fig. & 7 figs. on 2 pls. [Numerous refs.]

A summary of the results obtained and conclusions drawn from work done on the conditions which determine the sensitivity of motile *Salmonella* to phage $\phi\chi$ has already been reported in a letter to *Nature* [this *Bulletin*, 1961, v. 36, 1067.]. This paper presents the experimental details, together with electron micrographs and extensive tables of results. *Janice Taverne*

YAMAMOTO, N. & ANDERSON, T. F. **Genomic Masking and Recombination between Serologically Unrelated Phages P22 and P221.** *Virology.* New York. 1961, Aug., v. 14, No. 4, 430–39, 3 figs. [15 refs.]

"The bacteriophage P22 has a short tail with a hexagonal base plate but no contractile sheath. It is not adsorbed on a mutant strain (*St/22*) of its host *Salmonella typhi-murium* (*St*). A mutant P22*h*, forming faint plaques on *St/22* and clear plaques on *St*, is indistinguishable morphologically from P22. Preparations of P22 also contain a small proportion of a long-tailed phage, P221, which forms plaques on *St/22* but not on *St*, by which it is not adsorbed. Different strains of P22, containing markers like c^+, c_1 and c_2 that affect lysogenization, produce P221 strains with corresponding markers. Neither P22 nor P22*h* cross reacts serologically with P221. However, mixed infection of *St/22* by P22*h* and P221 produces masked genomes: particles carrying P22*h* genomes in P221 capsids and P221 genomes in P22*h* capsids. Moreover, P22*h* markers can be transferred to P221 genomes and vice versa. The existence of these stable hybrids may indicate that P221 represents a morphologically and serologically distinct mutant of P22. Alternatively, there may be present in *St* a defective prophage whose defects can be rectified by recombination with P22 to yield P221."

SWORD, C. P. & PICKETT, M. J. **The Isolation and Characterization of Bacteriophages from *Listeria monocytogenes*.** *J. General Microbiol.* 1961, June, v. 25, No. 2, 241–8, 1 fig. on pl. [37 refs.]

The isolation of a phage specific for *Listeria monocytogenes* was described by SCHULTZ [*Stanford Med. Bull.*, 1945, v. 3, 135; this *Bulletin*, 1946, v, 21, (147)]. To investigate the occurrence of these phages, 123 strains of *L. monocytogenes* from many different sources were irradiated with UV light and spotted onto 52 strains derived from various animal hosts and geographical areas, and belonging to several serological groups. Lysis occurred with 43 of the strains, but phages were only obtained from 12, the lysis occurring with the remaining 31 apparently being caused by the release of a colicine-like substance. 149 bacterial strains were tested for their sensitivity to 11 of the phages and 22 of them were found to be totally insensitive. The rest were classified into 8 phage types. Phage sensitivity was not related to animal source or geographical origin but showed good correlation with serological type. The phages may therefore be useful in epidemiological work, and it is suggested that a polyvalent pool of 3 of the phages could be used for identifying members of the genus.

Janice Taverne

VIRUSES

The order in this section is:—**General; Psittacosis-Lymphogranuloma group; Pox group; Respiratory group; Reovirus group; Enteric group; Arthropod-borne group; Others.**

MAGRATH, D. I., RUSSELL, Kate & TOBIN, J. O'H. **Vacuolating Agent.** *Brit. Med. J.* 1961, July 29, 287–8.

Many batches of renal tissue culture from rhesus or cynomolgus monkeys contain a virus which produces no visible effect in the original cultures, but which induces rapid cytopathic changes with vacuolation on passage to tissue cultures from kidneys of vervet monkeys. The interest of this virus agent lies in the fact that batches of poliovirus vaccine and adenovirus vaccine prepared in monkey kidney may contain vacuolating virus; vaccinated persons have been shown to develop anti-vacuolating agent antibody.

The original isolation of this virus by SWEET and HILLEMAN [this *Bulletin*, 1961, v. 36, 506, 1153] has now been confirmed in Britain by the present authors and the present paper reports some observations with 3 newly isolated strains.

The prototype American strain No. 776 (now classified as simian virus SV40), a second strain LV2, isolated from an American batch of Sabin vaccine used in Britain, and the 3 local isolates showed no antigenic differences in cross-neutralization tests with specific rabbit antisera in vervet monkey kidney cultures.

In a group of schoolboys given inactivated poliovirus vaccine, 11/12 sera from individuals given 3 doses of vaccine and 3/8 given 2 doses contained antibody to vacuolating agent (SV40).

A group of infants aged 6 to 12 months had received an American batch of live poliovirus vaccine containing 10^3–10^4 TCD50/ml. of SV40 virus in each component; none of 25 post-vaccination sera contained antibody to SV40 virus.

Rabbits inoculated with 2–4 doses of British live poliovirus vaccine did not develop anti-SV40 antibody.

Faecal extracts from 19 children who had been given the American live poliovirus vaccine were inoculated into vervet monkey tissue cultures at various intervals after vaccination; no vacuolating agent was found.

It was found that about 20% of the rhesus monkeys used in the authors' laboratory for tissue culture contained vacuolating agent, but virus was not found in 49 vervet monkeys.

These results suggest that there is definite risk of SV40 virus contaminating virus vaccines prepared in monkey kidney tissues; in live vaccines given by mouth SV40 appears not to be infective or immunogenic, but in formalin-inactivated vaccines the concentration is sufficiently high to induce an immune response.

Derek Hobson

JOHNSTON, P. B. **A Second Immunologic Type of Simian Foamy Virus: Monkey Throat Infections and Unmasking of Both Types.** *J. Infect. Dis.* 1961, July–Aug., v. 109, No. 1, 1–9, 3 figs. [19 refs.]

CHANY, C., with the technical assistance of F. ROBBE-FOSSAT & F. FOURNIER. **An Interferon-Like Inhibitor of Viral Multiplication from Malignant Cells (the Viral Autoinhibition Phenomenon).** *Virology.* New York. 1961, Apr., v. 13, No. 4, 485–92, 5 figs.

Cytopathic changes and viral multiplication of parainfluenza 3 virus in KB cells were greatest when the multiplicity of infection was of the order of 0·01; when the multiplicity was almost 1 no cellular changes or viral multiplication occurred. Single-step growth curves showed that a 10-fold decrease of virus yield occurred when the initial virus inoculum was increased 10-fold.

Further experiments were designed to show if this effect was due to the production of an interferon-like product during viral growth. KB cells in which a carrier state had been induced with parainfluenza 3 were compared with normal KB cells, and with KB cells infected 48 hours previously with parainfluenza 3, for their ability to support multiplication of poliovirus MEF1. Inhibition of poliovirus was much greater in KB cells freshly infected with parainfluenza than in the carrier culture, though in all 3 cell systems the number of poliovirus particles adsorbed was equal.

The interfering substance could be obtained from KB cells infected with parainfluenza 3 by centrifugation of tissue culture fluid at 30,000 r.p.m. for 2 hours in a Spinco No. 40 rotor. Alternatively, the substance could be obtained by dialysis at *p*H 2 and concentrated by polyvinyl pyrrolidone. Such preparations were active in protecting monkey kidney and human amnion cultures but not KB cells against MEF1 challenge.

Other tumour cell lines (HEP2 and PO-HA) were as effective as KB in producing the interfering substance.

It was shown that the material was not inactivated by specific parainfluenza 3 antiserum or over a *p*H range 2–8. Its activity was not mediated *via* the fall in *p*H due to the metabolism of virus-infected cells. In short, this material has many properties in common with interferon [ISAACS and LINDENMANN, this *Bulletin*, 1957, v. 32, 1203].

Derek Hobson

VOISIN, C., SAMAILLE, J. & AERTS, C. Mise en évidence de l'effet cytotoxique de certains virus par l'observation microcinématographique de l'exsudat péritonéal provoqué chez le cobaye. [**Determination of the Cytotoxic Effect of Certain Viruses by Photomicrographic Studies of Artificially Induced Peritoneal Exudate in Guineapigs**] *C.R. Soc. Biol.* 1961, v. 155, No. 1, 90–93, 1 fig.

In an attempt to differentiate cytotoxic effects of viruses on cells from cytopathic changes due to virus growth within the cells, the authors studied the activity of various human viruses in guineapigs which appear to be insusceptible to infection.

The intraperitoneal injection of Hanks saline or normal allantoic fluid alone resulted in a leucocytic exudate which was predominantly polymorphonuclear in the early stages. From 20 hours after injection, the polymorph count fell progressively but these cells were replaced by increasing numbers of macrophages (histiocytes); very few lymphocytes appeared late in the process.

When tissue culture fluids or allantoic fluids containing viruses were injected, a greater amount of exudate occurred but the cellular constitution was not significantly different from that in normal animals either in time of appearance or numerically. However, photomicrographic studies showed marked differences from normal leucocytic behaviour. Neutrophil polymorphs became rounded, enlarged and immobile; cytoplasmic vacuolation and loss of granules occurred. Many polymorphs were phagocytosed by macrophages. Eosinophils and lymphocytes did not seem to be affected, but the macrophages showed changes similar to those of neutrophil polymorphs.

These changes were reduced in specifically-immunized animals, or where heat-inactivated virus suspensions were used.

Viruses tested included influenza A, A^1, and B, adenovirus type 5, parainfluenza virus type 3, and Mahoney and MEF1 strains of poliovirus. Similar changes were produced by all strains. *Derek Hobson*

MORGAN, C., RIFKIND, R. A., HSU, K. C., HOLDEN, Margaret, SEEGAL, Beatrice C. & ROSE, H. M. **Electron Microscopic Localization of Intracellular Viral Antigen by the use of Ferritin-Conjugated Antibody.** *Virology.* New York. 1961, June, v. 14, No. 2, 292–6, 2 figs.

TANAMI, Y. & POLLARD, M. **Development of a Strain of Psittacosis Virus partially resistant to 5-Fluorouracil in a Tissue Culture System.** *Proc. Soc. Exper. Biol. & Med.* 1961, July, v. 107, No. 3, 648–51, 1 fig. [16 refs.]

"A strain of psittacosis virus (TTF) developed resistance to 5-fluorouracil (FU) after serial passages of the original FU-sensitive virus in tissue culture cells with small concentration of FU in the medium. The FU-resistant strain of TTF virus multiplied and produced more than 10^5 infective units per ml in presence of 2μg FU/ml, at which level FU suppressed the original wild-type TTF virus completely. Reversion of character from FU-resistance to FU-sensitivity following serial passages in FU-free medium was not observed. This suggests that the acquisition of FU-resistance is due to certain gene mutation(s), rather than to enzymatic adaptation."

SMITH, K. O. & SHARP, D. G. **Interaction of Virus with Cells in Tissue Cultures. III. Factors influencing Yield of Vaccinia Virus from L Cells.** *Virology.* New York. 1961, June, v. 14, No. 2, 267–75, 8 figs. [10 refs.]

The counting of vaccinia virus particles from disrupted L cells by electron microscopy was made easier when the cell debris was treated enzymically. It was found that as the multiplicity of infection was increased, the time of appearance of new virus was shortened. The greatest yield of virus particles per cell (about 9,000) was associated with an infection multiplicity of 50. The rate of virus particle production was not affected by multiplicity. The authors think that their results are evidence for replication of vaccinia virus at several sites within a cell [CAIRNS, this *Bulletin*, 1961, v. 36, 304].

[See also *ibid.*, 1961, v. 36, 87, 944.]

Colin Kaplan

LEBLOIS, J., SAMAILLE, J. & AERTS, C. Effet cytopathogène du virus vaccinal sur différents types de cultures cellulaires. [**Cytopathogenic Effect of Vaccinia Virus on Different Culture Cells**] *C.R. Soc. Biol.* 1961, v. 155, No. 1, 93–7. [14 refs.]

The authors used one strain of vaccinia virus to infect cultures of 4 different cells—HeLa, KB, human amnion and primary monkey kidney. Monolayers grown on cover-glasses were examined after staining by several methods or by phase contrast microscopy. They found 2 types of inclusions—cytoplasmic in uninfected control cultures, and juxtanuclear in infected cultures. The second type were shown more clearly by staining with Victoria blue than by any other stain they used. The Feulgen reaction of the specific inclusions was more often negative than positive; and when positive was only feebly so. The authors think this may be explained in terms of the intracellular development of the virus particles. There is also a brief description of the cytopathic changes seen in infected cultures.

[See also this *Bulletin*, 1960, v. 35, 510.]

Colin Kaplan

CABASSO, V. J., MOORE, I. F. & STEBBINS, M. R. **Proposed Potency Testing of Smallpox Vaccine. II. Comparative Titration in Rabbits, Chick Embryos and Tissue Culture.** *J. Immunology.* 1961, July, v. 87, No. 1, 46–8. [13 refs.]

The potencies of 4 batches of calf lymph smallpox vaccine and 7 of chick embryo smallpox vaccine were tested by scarification of rabbit skin, inoculation of rabbit kidney cell monolayer cultures and inoculation of chick embryos. All 3 methods detected the only vaccine which was below the permitted potency. The authors think that titration of smallpox vaccines of any given strain in rabbit kidney cell monolayers would be acceptable if a correlation were shown between the titre in tissue culture and the "take" rate in the field.

[For part I, see this *Bulletin*, 1957, v. 32, 1111.]

Colin Kaplan

ANDERSON, W. A. & KILBOURNE, E. D. **Immunization of Mice with Inactivated Herpes Simplex Virus.** *Proc. Soc. Exper. Biol. & Med.* 1961, July, v. 107, No. 3, 518–20, [10 refs.]

"Ultraviolet inactivated herpes simplex virus prepared in rabbit kidney cell cultures was injected intravenously

and intraperitoneally into mice. The majority of mice so immunized survived a 1000 LD_{50} intracerebral herpes simplex virus challenge and were shown to possess neutralizing antibody against the virus. These findings are contrary to the findings of studies in which inactivated allantoic fluid virus was used as antigen. However, they are in agreement with early experiments which employed inactivated herpes simplex virus prepared in mouse or rabbit brain and a recent report in which antigen was also prepared in rabbit kidney cell culture."

ANDERSON, W. A., MARGRUDER, B. & KILBOURNE, E. D. **Induced Reactivation of Herpes Simplex Virus in Healed Rabbit Corneal Lesions.** *Proc. Soc. Exper. Biol. & Med.* 1961, July, v. 107, No. 3, 628–32, 1 fig.

"Herpes simplex virus was inoculated into corneas of 8 rabbits with the induction of herpetic keratitis which proceeded to heal. The animals were then sensitized to horse serum and an Arthus reaction was induced in the healed cornea. Herpes simplex virus was repeatedly recovered in rabbit kidney cell culture from swabbings taken from these corneas. This phenomenon was observed 7 times in 19 attempts at induction. While there were several instances of spontaneous virus release, none occurred during the 14 day post-Arthus period in the unchallenged eyes of animals in which bilateral infection had been induced previously."

GRESSER, I. & ENDERS, J. F. **The Effect of Trypsin on Representative Myxoviruses.** *Virology.* New York. 1961, Apr., v. 13, No. 4, 420–26, 1 fig. [23 refs.]

Various myxoviruses were incubated with trypsin for 1 hour at 37°C. and titrated in tissue culture after the addition of soya bean inhibitor. There were three distinct modes of response: in group I, haemagglutinin was enzyme-resistant for influenza A, B, C, NDV and CA viruses and with all but influenza B there was no loss in infectivity; in group II, infectivity was rapidly destroyed whereas the haemagglutinin was reduced only moderately or not at all—this group included HA1 (parainfluenza 3 virus) and HA2 (parainfluenza 1 virus); Sendai virus behaved similarly, except for a small residual infectivity. In group III loss of infectivity was considerable but incomplete, whereas the haemagglutinin was totally destroyed. Only mumps virus showed this pattern of behaviour.

The residual infectivity of mumps was neutralized by specific antiserum, and in both mumps and Sendai, ribonuclease failed to remove the residual infective moiety, suggesting that this is due to resistant variant whole virus.

Trypsinization did not affect the complement-fixing properties of live or heat-inactivated influenza A, mumps or HA2 viruses.

A strain of herpes simplex, similarly trypsinized, showed a marked fall in infectivity when tested in tissue culture or in animals.

It is probable that these modes of response to trypsin represent differences in biological interrelationships of the myxoviruses, and may be of help in classification within the group. *Derek Hobson*

HOYLE, L., HORNE, R. W. & WATERSON, A. P. **The Structure and Composition of the Myxoviruses. II. Components released from the Influenza Virus Particle by Ether.** *Virology.* New York. 1961, Apr., v. 13, No. 4, 448–59, 10 figs. [16 refs.]

Virus particles of the DSP strain of influenza virus concentrated by red cell adsorption-elution techniques from allantoic fluid cultures were treated with phosphotungstic acid. Electron microscopy showed predominantly spherical particles 800–1,000 Å in diameter. No internal structure was seen, but the surface of the particle consisted of an even arrangement of radially arranged rods 100 Å long, and in some particles a continuous membrane-like layer could be seen below this outer zone.

Normal chorioallantoic cells are known to detach particles very similar to those of influenza virus [HOYLE, this *Bulletin*, 1955, v. 30, 181]. Similar electron microscopic study showed a greater variation in size than the virus particles and no evidence of the radial rod-like surface structure.

In virus particles which had been partially disintegrated by treatment with ether, the surface layers had disappeared and an inner structure was revealed, consisting of a helical component 6,000–8,000 Å in length, similar to those already described for other myxoviruses [HORNE *et al.*, *ibid.*, 1960, v. 35, 1142, and HORNE and WATERSON, *J. Molecular Biol.*, 1960, v. 2, 75; this *Bulletin*, 1960, v. 35, (935)].

Purified soluble antigen obtained from DSP virus by ether disintegration followed by adsorption with red cells was found to consist of elongated particles 90–100 Å in diameter; the length was variable, with a mean of 600 Å. In structure these filaments appeared to be helical consisting of a double chain in which each turn of the helix contained 5 or 6 subunits.

Purified haemagglutinin did not have as precise or constant a structure as the soluble antigen, and the appearance varied according to the method of preparation. Spherical structures 300–500 Å in diameter were found; these resembled rosettes and appeared to consist of the surface rods seen in the intact virus particles. In addition, larger components, 1,000–15,000 Å across were found; these resembled partly disrupted virus membranes, with no precisely defined surface structure.

Derek Hobson

CHOPPIN, P. W., MURPHY, J. S. & STOECKENIUS, W. **The Surface Structure of Influenza Virus Filaments.** *Virology.* New York. 1961, Apr., v. 13, No. 4, 548–50, 2 figs.

In electron microscopy studies of various influenza strains negatively stained with phosphotungstate, the surface of the spherical virus particles was covered with projections 80–100 Å in length, similar to those described in influenza and other myxoviruses by HORNE *et al.* [this

Bulletin, 1960, v. 35, 1142]. Filamentous viral forms were also found, in the present study only, to have similar projections in every strain tested, and in some filaments the longitudinal central region appeared to be hollow. *Derek Hobson*

WATERSON, A. P., JENSEN, K. E., TYRRELL, D. A. J. & HORNE, R. W. **The Structure of Parainfluenza 3 Virus.** *Virology*. New York. 1961, July, v. 14, No. 3, 374–8, 3 figs.

Two strains of parainfluenza type 3 (HA1) virus, one isolated from cattle, were examined by electron microscopy after phosphotungstic acid treatment. Both strains showed similar particles 1,400–2,500 Å in diameter, and disrupted particles showed helixes 150 Å in diameter, with a hollow core. The outer layer contained some irregular projections, but these were far less conspicuous than in influenza virus strains [HORNE *et al.*, this *Bulletin*, 1960, v. 35, 1142]. In general the appearances of parainfluenza type 3 were similar to those of the serologically related Sendai and mumps viruses and to NDV, although particle size was rather smaller and the helix more compact in parainfluenza 3. This resemblance to other "parainfluenza" viruses was greater than to the "true" influenza group of myxoviruses, and the authors suggest that morphological features are sufficiently distinct to be of value in classification of the group. *Derek Hobson*

KETLER, A.; HAMPARIAN, V. V.; HILLEMAN, M. R.; MCCLELLAND, L.; HAMPIL, B.; POTASH, L.; WASHKO, F. V. **Laboratory and Field Investigations of Bovine Myxovirus Parainfluenza 3 Virus and Vaccine. I. Properties of the SF-4 (Shipping Fever) Strain of Virus** [KETLER, HAMPARIAN & HILLEMAN]. *J. Immunology*. 1961, Aug., v. 87, No. 2, 126–33. [20 refs.] **II. Development and Appraisal of Potency of SF-4 (Shipping Fever) Virus Vaccine** [MCCLELLAND, HAMPIL, HAMPARIAN, POTASH, KETLER & HILLEMAN]. *Ibid.*, 134–8, 1 fig. **III. Evaluation of an SF-4 (Shipping Fever) Virus Vaccine in Cattle** [HAMPARIAN, WASHKO, KETLER & HILLEMAN]. *Ibid.*, 139–46.

KATO, N., MATSUMOTO, T., MAENO, K. & OKADA, A. **A New Strain of the Hemagglutinating Virus of Japan isolated from Mice.** *Biken's J.* Osaka. 1961, Mar., v. 4, No. 1, 59–62.

FRANKLIN, R. M. **Comparison of Assays for Mengovirus and Reovirus-3.** *Proc. Soc. Exper. Biol. & Med.* 1961, July, v. 107, No. 3, 651–3, 1 fig.

"Reovirus-3 was passaged in L-cells where it grew and produced a cytopathic effect. A plaque assay in L-cells is described for this virus and compared with the plaque assay for Mengovirus."

ALBANO, A. Über einige einfache Methoden zur Konzentration von Viren. **[Some Simple Methods of Virus Concentration]** *Zent. f. Bakt.* I. Abt. Orig. 1961, v. 181, No. 4, 451–5. [18 refs.]

Two simple methods for concentrating types 1, 2 and 3 poliomyelitis virus, types B1 and B3 Coxsackie virus and types 4 and 6 ECHO virus from the supernatant fluids of infected monkey kidney and KB cell cultures. (1) The fluid is clarified by low-speed centrifugation and 100–200 cc. are placed in a Cellophane dialysis tube which is suspended in a 10-litre glass vessel with an opening at the top and at the side near the bottom. Air is drawn through the vessel by means of a pump attached to the lower opening, and the virus-containing fluid is thus concentrated by pervaporation in the aspirated current of air. A precipitate forms which contains the virus; this may be resuspended in a still smaller volume of fluid, or the virus may be recovered by elution. (2) The clarified culture fluid is placed in a Cellophane tube in a 250 cc. glass cylinder and dialysed against polyethylene glycol.

By both methods it was possible to achieve a 40–100-fold reduction in volume over a period of 15–16 hours with an accompanying rise in titre of about 2 log units. *D. J. Bauer*

QUERSIN-THIRY, L. **Interaction between Cellular Extracts and Animal Viruses. I. Kinetic Studies and some Notes on the Specificity of the Interaction.** *Acta Virologica*. Prague. 1961, May, v. 5, No. 3, 141–52, 6 figs.

HOLLAND and MCLAREN [this *Bulletin*, 1959, v. 34, 953] showed that after disruption of cells susceptible to enteroviruses the cellular debris inactivates those enteroviruses. They believe the virus inactivator is the specific cell receptor. In this study frozen and thawed cell extracts, or sonically disrupted cells, were examined for their capacity to inactivate poliomyelitis (Mahoney type 1, MEF1 type 2, Saukett type 3), Western equine encephalitis and Newcastle disease viruses, and others. The viruses were inactivated by debris of cells which were sensitive to the viruses. There was a rapid initial rate of virus inactivation to 10–20% survival and thereafter a very slow inactivation with a residual proportion of persisters. With WEE and NDV especially, there was evidence that the virus cell debris inactivation was reversible. The elution of NDV from HeLa cell debris was largely prevented by treatment of the debris with metaperiodate.

The persistent fraction of virus particles was not due to exhaustion of cell inactivator since fresh virus was still inactivated and additional cell debris did not increase the virus inactivation. The pattern of inactivation is similar, though less intense, to that observed with neutralizing sera. After treatment with both serum and cell debris fewer virus particles survive than if either is used alone. The proportion of virus susceptible to serum in untreated preparations and preparations treated with cell debris is similar. A limited experiment is reported on the effects of cell debris from freshly chopped monkey kidney, primary trypsinized kidney cells, grafted kidney

cells and HeLa cells on poliomyelitis, Coxsackie A9 and B1 and ECHO 9 viruses. These results show in general that susceptible cells yield a virus inactivator on disruption. Thus, fresh monkey kidney has little or no inactivator for poliovirus or Coxsackie B1 whereas graft or primary trypsinized cells have. ECHO 9 is not significantly inactivated by HeLa cell debris but is by fresh monkey kidney and trypsinized primary cells and grafted cells.

[The author of this very interesting paper is careful not to call the inactivating substance in cell debris "receptor substance" but see the series of papers by HOLLAND and his colleagues, *ibid.*, 953, 1193; 1961, v. 36, 306; and below.] *A. J. Beale*

HOLLAND, J. J. & MCLAREN, L. C. **The Location and Nature of Enterovirus Receptors in Susceptible Cells.** *J. Exper. Med.* 1961, Aug. 1, v. 114, No. 2, 161–71, 4 figs. [11 refs.]

The authors [this *Bulletin*, 1959, v. 34, 953] have previously shown that susceptible cells have a receptor substance capable of binding enteroviruses. This substance is destroyed by ether, chloroform and proteolytic enzymes. It was found that enterovirus (poliovirus type 1 and Coxsackie B1) receptor of susceptible cells (HeLa, primary human amnion and monkey kidney cells) was present in the microsome fraction of disrupted cells. The amount of receptor in disrupted cells exceeded that in intact ones, suggesting (but not proving) that the receptor may be present inside as well as at the surface of the cells. Receptor substance was thought to be a lipoprotein. All attempts to get it into solution failed; it was destroyed by strong acid or alkali, N-butanol, desoxycholate and sodium dodecyl sulphate. Formaldehyde, phenol and high concentrations of urea and guanidine also destroyed the receptor.

[See also the paper by Quersin-Thiry, above.] *A. J. Beale*

SPEIR, R. W. **Thermal Stability of Mengo and Poliovirus in Hypertonic Salt.** *Virology.* New York. 1961, July, v. 14, No. 3, 382–3, 2 figs.

The Mengo strain of encephalomyocarditis virus and the MEF1 strain of poliovirus type 2 were suspended in 0·05 M phosphate-buffered saline solutions, with final concentrations of sodium chloride of 2 M or 0·1 M.

The virus suspensions were incubated at 56°C. and samples withdrawn for assay at serial intervals.

In 0·1 M NaCl, the mouse-infectivity titre of Mengo virus fell 100,000-fold after 1 hour at 56°C. and viral haemagglutinin was completely destroyed; in 2 M NaCl less than a 100-fold loss of infectivity occurred during the first hour, and haemagglutinin decreased far more slowly.

Poliovirus incubated in 0·1 M NaCl decreased in titre from approximately 10^7 TCD50 in 1 ml. to less than $10^{0.5}$ TCD50 in 1 ml. in 1 hour, whereas incubation in 2 M NaCl reduced the initial count only to $10^{4.5}$ TCD50 per ml. after 2 hours' incubation. *Derek Hobson*

LEDINKO, Nada & HIRST, G. K. **Mixed Infection of HeLa Cells with Polioviruses Types 1 and 2.** *Virology.* New York. 1961, June, v. 14, No. 2, 207–19, 3 figs. [18 refs.]

A series of elegant experiments on mixed infection of HeLa cells in mass culture or in isolation with poliovirus types 1 and 2 is described. When both viruses are used at a multiplicity of 5, 80–90% of the progeny are neutralizable with both type 1 and type 2 antiserum. This is an example of phenotypic mixing. Even after 1 cycle of additional growth the single genotype exerts itself in the production of either type 1 or type 2 particles, thus excluding genetic recombination. Aggregation of particles is not the explanation since double neutralizable particles have the same "single hit" type of UV inactivation curve as the parental monotypic poliovirus. The yield of doubly neutralizable particles was high both in single cells and mass cultures and was in excess of expected values calculated from adsorption studies.

Two hypotheses were considered. First, that larger cells with larger yields might, because of their greater surface area, more frequently become infected with both serotypes. Direct experiment showed that large yielders and small yielders among single cells had the same proportion of doubly neutralizable particles. About 20% of the cells do not produce virus, presumably because they fail to adsorb it. However, there is still an excess yield of double phenotypes when the multiplicity of infection is corrected upwards for this factor. The other possibility considered is that virus reactivation explains the excess of doubly neutralizable particles. There are plenty of inactive particles in the poliovirus preparations to account for the observed numbers of such particles but attempts to produce direct evidence for viral reactivation failed. *A. J. Beale*

DARNELL, J. E., Jr. & EAGLE, H. **The Biosynthesis of Poliovirus in Cell Cultures.** *Advances in Virus Res.* 1960, v. 7, 1–26. [Numerous refs.]

Only just over a decade ago poliovirus was one of the most difficult viruses to study and poliomyelitis a menacing epidemic disease. Now poliovirus is increasingly the virus of choice for fundamental quantitative studies of virus replication. This interesting paper reviews comprehensively the work on the biosynthesis of poliovirus up to the end of 1959 and, less completely, the work in 1960. Poliovirus is particularly valuable since it is an RNA virus which can readily be purified and accurately titrated. Moreover, some of the cell cultures used to grow the virus have also been extensively studied. Thus HeLa cells can be grown in suspension starting from a single clone of cells of known nutritional requirements. Poliovirus and the HeLa cell S-3 line therefore form an excellent system for such studies.

[This paper can be thoroughly recommended as a review of past accomplishments and as a springboard for future experiments.] *A. J. Beale*

KROOTH, R. S. & TJIO, J. H. **The Biosynthesis of Poliovirus by Euploid "Fibroblasts" of Non-neoplastic Origin.** *Virology*. New York. 1961, June, v. 14, No. 2, 289–92, 1 fig. [12 refs.]

Fibroplastic euploid cell lines can be derived from biopsies of human skin and maintained in culture for long periods. Since such cells might overcome some of the difficulties in the production of virus vaccines 3 such lines were compared with HeLa cells in susceptibility to polioviruses. It was found that the yield per cell of Mahoney type 1 poliovirus in a single cycle experiment was similar to that in HeLa cells for 2 cell lines. The yield exceeded 100 plaque-forming units per cell. On the other hand, the yield from monolayer cultures tended to be lower, probably mainly because there were fewer cells with euploid lines than with HeLa cells. *A. J. Beale*

TAYLOR-ROBINSON, D., ZWARTOUW, H. T. & WESTWOOD, J. C. N. **The Oxygen Requirement for Poliovirus Replication in Concentrated Suspensions of ERK Cells.** *Brit. J. Exper. Path.* 1961, Aug., v. 42, No. 4, 317–23, 1 fig.

This paper is a continuation of the authors' studies on methods of producing high titre poliovirus in embryo rabbit kidney cells [WESTWOOD *et al.*, this *Bulletin*, 1960, v. 35, 937; ZWARTOUW *et al.*, *ibid.*, 1144]. Methods capable of producing virus titres of up to 10^{10} are described. The yield of virus per cell was 100–300 plaque-forming units by the techniques used. When 10^7 cells per ml. were used, oxygen was the limiting factor in a saline medium but it could be replaced by 0·4% glucose. Maximum virus production was achieved with 5–95% oxygen when 10^7 cells per ml. were employed, but with 10^6 cells per ml. the virus yield was slightly inhibited by oxygen concentrations above 50%. 10^8 cells per ml. required still more oxygenation (95% oxygen with vigorous agitation on a rotary shaker). The usual medium was Earle's saline with 0·11% sodium bicarbonate, but for greater cell concentration, from 10^7 to 10^8, the concentration had to be increased to 0·22–0·44% sodium bicarbonate. Most experiments were done in 10 ml. amounts but the volume in which 10^7 cells per ml. were used was successfully scaled up to 1·5 litres with culture depths up to 5 cm. under a gas phase of 5% CO_2 in oxygen. Deeper cultures could not be obtained without oxygen by the addition of 0·4% glucose, but the addition of glucose and oxygen enabled the depth of cultures to be increased 2–3-fold.

The implications of this work for the large-scale production of poliovirus for a diagnostic antigen, chemical investigations and vaccine production are discussed. It is said that similar work with primary monkey kidney cells is shortly to be published. *A. J. Beale*

EVANS, C. A., GRAHAM, C. B., Jr., HOSHIWARA, I. & OH, J. O. **Patterns of Increase and Spread of Polioviruses in Monkeys after Inoculation into Traumatized Tissue.** *Proc. Soc. Exper. Biol. & Med.* 1961, May, v. 107, No. 1, 97–101, 2 figs. [10 refs.]

An earlier paper by these workers [EVANS and HOSHIWARA, this *Bulletin*, 1955, v. 30, 1031] reported that inoculation of poliovirus into healing skin wounds of cynomologus monkeys resulted in a local increase of virus, and dissemination to other areas.

In the present experiments 4 strains of poliovirus type 1 were selected because of known differences in origin and virulence. The Mahoney strain was compared with the avirulent LSc strain [LI and SCHAEFFER, *ibid.*, 371], with the Iberia strain isolated from a healthy child in a community where clinical poliomyelitis was not prevalent [FOX *et al.*, *ibid.*, 1958, v. 33, 931], and with the Chesterfield Inlet strain from a violent epidemic of Eskimos [PEART, *ibid.*, 1950, v. 25, 357].

In each of a series of cynomolgus monkeys, 5 areas of 1 sq. cm. of skin were excised and 3 days later the bases of 3 lesions were inoculated with varying amounts of virus. At serial intervals exudate from the wound was collected by a standardized procedure, and venous blood was taken, for virus assay.

The minimum infective dose varied from 60 TCD50 for Mahoney virus to 4,000 TCD50 for the LSc strain. Only the LSc strain failed to spread to distant uninoculated lesions; with the other strains, rises in virus titre occurred almost simultaneously in all lesions, inoculated and uninoculated, and reached similar levels. Paralysis occurred in both monkeys inoculated with Mahoney virus, 1 of 2 animals given Chesterfield Inlet virus, 1 of 4 given Iberia virus but in none of the monkeys inoculated with LSc virus.

All skin wounds healed normally with no signs of infection, but in most cases the poliovirus concentrations were much greater in the wound exudate than in the blood.

The authors suggest that extraneural proliferation of poliovirus was occurring in the connective tissue base of the wounds, and that the preliminary trauma in these regions might have induced virus susceptibility in normally-insusceptible types of cell. They further suggest that this method of studying extraneural multiplication of polioviruses may be of use in selecting virus strains suitable for oral vaccines. *Derek Hobson*

HATCH, M. H., KALTER, S. S. & AJELLO, Gloria W. **Identification of Poliovirus Isolates with Fluorescent Antibody.** *Proc. Soc. Exper. Biol. & Med.* 1961, May, v. 107, No. 1, 1–4.

This paper reports the application of immuno-fluorescence techniques to the identification of polioviruses; similar diagnostic methods for influenza have been described by LIU [this *Bulletin*, 1957, v. 32, 229].

Globulins prepared from monkey immune poliovirus typing sera were conjugated with fluorescein isothiocyanate or isocyanate.

85 faecal specimens were inoculated into monkey kidney tissue culture; where cytopathic changes occurred, tubes showing + or ++ effects were examined by removing tissue cells from the glass with versene, making air-dried smears on glass slides, and staining with specific antipoliovirus conjugates. Of 38 specimens containing poliovirus, 34 were correctly identified by the rapid fluorescence method, though all 38 were identified

by conventional neutralization tests. 18 faecal specimens yielding enteroviruses other than poliovirus did not give fluorescent staining with the three test reagents.

[The practical disadvantage of this technique is the use of direct fluorescence methods, where each type of antibody is separately conjugated with fluorescein isocyanate. It would be interesting to know why the authors did not use more flexible indirect fluorescence techniques where standard monkey typing antisera could be used in tests with a single conjugated anti-monkey serum.] *Derek Hobson*

VONKA, V. & ŽÁCEK, K. **Evaluation of Different Methods of Neutralizing Antibodies Estimation in Poliomyelitis.** *J. Hyg., Epidemiol., Microbiol. & Immunol.* Prague. 1961, v. 5, No. 2, 168–77. [12 refs.]

SABIN has noted that there is often a discrepancy between the antibody titre determined by the *p*H method and by the CPE inhibition technique. Titres are usually higher by the *p*H method and Sabin (*Spec. Publ. N.Y. Acad. Sci.*, 1957, v. 5, 113) has referred to these as low avidity antibodies. In this paper the fact that higher titres can be obtained by the *p*H method is confirmed. The authors conclude, however, that the CPE test as usually performed with a 1-hour neutralization time is an insensitive way of measuring neutralizing antibodies. They believe that this factor, together with the rather greater dilution employed in the cytopathic inhibition test compared with the *p*H method, is the most important reason for the lower titres by the CPE technique. They conclude that the CPE method of titration is inadequate owing to lack of sensitivity but do not think that it detects a different quality of antibodies. *A. J. Beale*

KHESIN, I. E., GENDON, Y. Z., LEVENBUK, I. S. & ROZINA, E. E. **Morphological Characterization of Poliomyelitis in Monkeys infected with Sabin's Attenuated Strains.** *Acta Virologica.* Prague. 1961, May, v. 5, No. 3, 133–6.

The authors describe the histological appearances in monkeys in which SABIN's strains of attenuated poliovirus were inoculated into the nervous system. These changes, they believe, are sufficiently characteristic to justify the description of a new marker, called M, for the morphological changes produced in the central nervous system. The chief feature is that the lesions are confined to the site of inoculation of the virus with minimal spread and that they are mainly vascular with little neuronal damage. *A. J. Beale*

SLONIM, D., MARES, I., DREVO, M., CINNEROVÁ, O. & MICHL, J. **Some Experiences with the Preparation of Inactivated Poliomyelitis Vaccine in Czechoslovakia. IV. The Preparation of the Vaccine.** *Acta Virologica.* Prague. 1961, May, v. 5, No. 3, 178–87, 2 figs. [22 refs.]

This is a valuable and detailed account of the method of manufacture of killed poliovaccine used in Czechoslovakia. The authors employ the classical Salk inactivation technique and the method they use only differs in detail from that employed by other manufacturers. The virus is filtered through a Seitz EKS1 filter before inactivation and then the monovalent pools are re-filtered through a Seitz EKS1 filter before being blended into the final vaccine. The authors note that by pre-treating the pads with gelatin they can avoid any loss of virus by adsorption on to the pads. Inactivation curves of the 3 types of virus are presented and they show that the inactivation rate differs significantly from the first order kinetics claimed for this process by Salk, but a more detailed analysis of this part of the problem is promised later. *A. J. Beale*

LENAHAN, Margaret F. & WENNER, H. A. **Propagation of Group A Coxsackie Viruses in Primary Human Amnion Cells. I. Cytopathic Changes produced by 5 more Serotypes.** *Proc. Soc. Exper. Biol. & Med.* 1961, July, v. 107, No. 3, 544–6. [11 refs.]

18 of 26 Coxsackie A viruses were found to produce CPE and to be serially propagated in human amnion cells. 14 produced unequivocal changes but for 4 viruses (types 3, 8, 12 and 16) the changes were less clear cut. 8 strains (types 1, 2, 4, 5, 6, 7, 19 and 22) did not produce CPE. Type 7 produced CPE in monkey kidney cells. Type 6 has been reported to grow in human amnion cells by LEHMANN-GRUBE and SYVERTON (*Fed. Proc.*, Wash., 1959, v. 18, 488) but this could not be confirmed. SLATER and SYVERTON [this *Bulletin*, 1950, v. 25, 1320] have been able to culture type 4 in minced mouse embryo cells. Thus far 5 Coxsackie A viruses have not been grown in tissue culture but the authors believe that these 5 will eventually yield. *A. J. Beale*

SCHMIDT, Nathalie J., FOX, Virginia L. & LENNETTE, E. H. **Immunologic Identification of Coxsackie A21 Virus with Coe Virus.** *Proc. Soc. Exper. Biol. & Med.* 1961, May, v. 107, No. 1, 63–5. [11 refs.]

Coe virus was first isolated in Lennette's laboratory [LENNETTE *et al.*, this *Bulletin*, 1959, v. 34, 397] from military recruits with mild respiratory illnesses, and its aetiological relationship to such infections has been shown in human volunteers [PARSONS *et al.*, *ibid.*, 1960, v. 35, 1057].

Coe virus does not produce cytopathic effects in monkey kidney tissue culture, but in continuous cell lines or human tissues cytopathic changes are closely similar to those of enteroviruses, which Coe virus resembles in ether resistance and in particle size [PEREIRA and PEREIRA, *ibid.*, 90]. Prototype strains of Coe virus cannot be propagated in suckling mice.

Coxsackie virus A21 was also first isolated in Lennette's laboratory in human embryo tissue culture, and the prototype Kuykendall strain was found to be variably virulent for suckling mice, producing flaccid paralysis with myositis.

In cross-neutralization tests, hamster immune sera to Coe and to Coxsackie A21 (Kuykendall) had virtually

the same end-points against either virus strain [no cross-adsorption studies are reported].

This paper presents further evidence that pathogenicity for suckling mice is not an absolute method of differentiating one group of enteroviruses from another, and suggests that the Coxsackie group of viruses should not be overlooked in epidemiological studies on respiratory disease. *Derek Hobson*

KAMITSUKA, P. S., SOERGEL, M. E. & WENNER, H. A. **Production and Standardization of ECHO Reference Antisera. I. For 25 Prototypic ECHO Viruses.** *Amer. J. Hyg.* 1961, July, v. 74, No. 1, 7–25. [40 refs.]

This is a long and detailed report on the production and standardization of reference sera against the first 25 ECHO virus serotypes. Sera to types 26 to 28 are also nearly ready for distribution. The value and limitations of these sera for neutralization, complement-fixation and haemagglutinin inhibition tests are described. All the antisera were produced in monkeys with the aim of obtaining sera which would be useful in complement-fixation as well as neutralization tests. Some of the antisera had low titres to various simian viruses. The reactions were specific for the most part, though cross-reactions occurred between ECHO 1, 8 and 12. ECHO 4 serum neutralized adenovirus type 8 and Coxsackie B4 was neutralized by several sera. Central nervous lesions occurred in some monkeys inoculated extraneurally with ECHO types 1, 2, 3, 4, 6, 10, 19 and 24.

[This is an extremely valuable piece of work which will earn the indebtedness of all who work with ECHO viruses. It should be read in the original.]

A. J. Beale

MARTIN, E. M.; MALEC, J.; SVED, S.; WORK, T. S.; FAULKNER, P.; VALENTINE, R. C.; COOTE, J. L. **Studies on Protein and Nucleic Acid Metabolism in Virus-Infected Mammalian Cells. I. Encephalomyocarditis Virus in Krebs II Mouse-Ascites-Tumour Cells** [MARTIN, MALEC, SVED & WORK]. *Biochem. J.* 1961, Sept., v. 80, No. 3, 585–97, 3 figs. [44 refs.] **2. The Isolation, Crystallization and Chemical Characterization of Mouse Encephalomyocarditis Virus** [FAULKNER, MARTIN, SVED, VALENTINE & WORK]. *Ibid.*, 597–605, 4 figs. & 1 pl. [40 refs.] **3. Methods for the Disruption of Krebs II Mouse-Ascites-Tumour Cells** [MARTIN, MALEC, COOTE & WORK]. *Ibid.*, 606–11. [20 refs.]

LIEBHABER, H. & TAKEMOTO, K. K. **Alteration of Plaque Morphology of EMC Virus with Polycations.** *Virology.* New York. 1961, Aug., v. 14, No. 4, 502–4, 1 fig.

TAKEMOTO, K. K. & LIEBHABER, H. **Virus-Polysaccharide Interactions. I. An Agar Polysaccharide Determining Plaque Morphology of EMC Virus.** *Virology.* New York. 1961, Aug., v. 14, No. 4, 456–62, 3 figs.

"Wild-type EMC virus produced minute plaques (1 mm at 4 days) on L cell monolayers with an occasional mutant which produced large plaques (8–10 mm at 4 days). A sulfated polysaccharide present in agar inhibited the growth of the minute-plaque former, but had no effect on the large-plaque mutant. In the absence of the agar polysaccharide, the minute-plaque former actually multiplied more rapidly than the mutant. Two other macroanions, polyglucose-SO_4 and heparin, were also inhibitory to the virus that formed small plaques."

BERDJIS, C. C., GLEISER, C. A., GOCHENOUR, W. S. & BERGE, T. O. **Virus Infection and X Radiation: a Comparative Study of Infection with an Attenuated Venezuelan Equine Encephalomyelitis Virus and of X Radiation.** *J. Infect. Dis.* 1961, July–Aug., v. 109, No. 1, 62–70, 10 figs.

"This study was undertaken to investigate damage to the lymphatic tissues and bone marrow produced in guinea pigs by an attenuated strain (TC-50) of Venezuelan equine encephalomyelitis virus (VEE) and by X rays (175 r, total body). The sequence of pathologic changes were compared by serial sacrifices (tables 1 and 2). Although neurotropic in principle, VEE virus acts as a viscerotropic agent on the 50th passage in guinea pig heart culture.

"VEE virus and X rays exert a selective effect upon the lymphatic organs and bone marrow. The effect of X rays was immediate and dramatic, whereas that of TC-50 was slower, especially in bone marrow. The thymus, markedly depleted in irradiated animals, seemed to be spared by this virus. Secondary depletion was observed at day 13 in the irradiated group and was absent in the TC-50 group."

HEARN, H. J., Jr. **Cross-Protection between Venezuelan Equine Encephalomyelitis and Eastern Equine Encephalomyelitis Virus.** *Proc. Soc. Exper. Biol. & Med.* 1961, July, v. 107, No. 3, 607–10. [13 refs.]

"Mice were capable of withstanding a large challenge dose of virulent Venezuelan equine encephalomyelitis virus and a substantial challenge dose of eastern equine encephalomyelitis virus after immunization with an attenuated 9t strain of VEE virus. This resistance was elicited after administration of the 9t strain by the intraperitoneal, subcutaneous, and respiratory routes, the latter being accomplished by short exposures to aerosols of the attenuated strain. Rabbits and guinea pigs, which were refractory to infections with EEE virus, were protected against lethal doses of the heterologous virulent VEE virus."

VAINIO, T., GWATKIN, R. & KOPROWSKI, H. **Production of Interferon by Brains of Genetically Resistant and Susceptible Mice infected with West Nile Virus.** *Virology.* New York. 1961, July, v. 14, No. 3, 385–7, 1 fig.

The role of interferon in infectious processes in the intact animal has already been considered by Isaacs and

his colleagues [Isaacs and Hitchcock, this *Bulletin*, 1960, v. 35, 1056] and by Hitchcock and Porterfield [*ibid.*, 1961, v. 36, 1070] and this paper presents further evidence that interferon can be elaborated *in vivo*.

Inbred BRVR and BSVS mice, which are respectively genetically resistant and susceptible to West Nile virus, were inoculated intracerebrally with a mouse-brain pool of the E 101 strain of West Nile virus. At serial intervals mice from each group were killed; brain emulsions were assayed for infective virus after centrifugation at 1,500 r.p.m., and again for interferon after Spinco centrifugation at 105,000 g for 45 minutes.

Interferon assays were performed on I cell monolayers infected with the Mengo strain of encephalomyocarditis virus, the brain extract being titrated in agar wells for inhibitory activity.

The yield of West Nile virus from brains of BRVR mice was much lower than from BSVS mice; interferon was produced in brains of the susceptible strain, but little or no activity was found in brains of BRVR mice.

These results suggest that the mechanism of genetic resistance to Arbor group B virus infections in BRVR mice is not mediated by an increased facility in interferon production. *Derek Hobson*

McLean, D. M., Walker, Selma J., Macpherson, L. W., Scholten, T. H., Ronald, K., Wyllie, J. C. & McQueen, E. Joan. **Powassan Virus: Investigations of Possible Natural Cycles of Infection.** *J. Infect. Dis.* 1961, July–Aug., v. 109, No. 1, 19–23.

"During 1959 and 1960 neutralizing antibody to Powassan virus was detected in serums from 5 of 23 chipmunks and 2 of 14 squirrels captured near Powassan, Ontario. No antibody was detected in 17 snowshoe hares despite heavy infestation with the tick *Haemaphysalis leporis palustris*.

"On Manitoulin Island during 1960, neutralizing antibody to Powassan virus was detected in serums from 5 of 178 snowshoe hares, 2 of 16 chipmunks, and 2 of 45 squirrels, suggesting that all these species may be reservoirs of virus. No vector of Powassan virus between wildlife and man has been incriminated as yet. Isolation of previously unrecognised viruses from 2 pools of *H. leporis palustris* removed from 4 hares suggests that this species may be a vector in natural cycles of infection with these viruses in ticks and snowshoe hares."

McIntosh, B. M., Kokernot, R. H., Paterson, H. E. & De Meillon, B. **Isolation of Spondweni Virus from Four Species of Culicine Mosquitoes and a Report of Two Laboratory Infections with the Virus.** *South African Med. J.* 1961, Aug. 5, v. 35, No. 31, 647–50. [11 refs]

"1. Nine strains of Spondweni virus were isolated in mice from 13,123 female mosquitoes collected in Tongaland, South Africa, in 1958.

"2. Four strains were isolated from *Aedes* (*Neomelaniconion*) *circumluteolus* (Theo.), 3 strains from *Mansonia* (*Mansonioides*) *africana* (Theo.), and one strain each from *A. cumminsi* ssp. *mediopunctatus* (Theo.) and *Eretmapodites silvestris*, Ingram and De Meillon.

"3. With the haemagglutination-inhibition, complement-fixation and neutralization tests, these strains were found to be immunologically similar to the strain of Spondweni virus isolated in Tongaland in 1955.

"4. The outbreak of Spondweni virus activity in mosquitoes in 1958 followed a 2-year period when the presence of this virus had not been detected in Tongaland.

"5. The non-arthropod host involved in the outbreak was not apparent.

"6. At the time that strains of Spondweni virus were being handled in the laboratory, 2 cases of illness occurred among laboratory personnel. Spondweni virus was isolated from one individual. The nature of the antibody response in the convalescent sera of both was studied with the neutralization, complement-fixation, and haemagglutination-inhibition tests."

Morzycka, Maria. Badania nad wirusem odry. [**Studies on Measles Virus**] *Archiwum Immunol. i Terapii Dośw.* Warsaw. 1960, v. 8, No. 4, 695–737, 13 figs. [82 refs.] English summary.

The behaviour of the Edmonston strain of measles virus has been studied in 7 cell lines. Multiplication through up to 9 passages was obtained in Detroit-6, Hep-2, KB, MKG (monkey kidney), HeLa, FL and Cyn (cynomolgus monkey heart) cells. There was a delay of up to 10 days in the appearance of a cytopathic effect on primary passage in the last 3 cell lines, but in the others the cytopathic effect appeared after 3–5 days. The appearances of the various cell lines infected with the virus are illustrated in photomicrographs. The highest titres (10^6 TCD50 per 0·1 ml.) were obtained with Detroit-6 cells.

By the inoculation of cultures of human amnion, monkey kidney and FL cells 14 strains of measles virus were isolated from 20 patients suffering from the disease; 3 strains were isolated from the throat, 2 from the blood and 9 from the stools.

The sera of 478 children and adults were examined in complement-fixation tests with measles antigen produced in Detroit-6 cells; titres of 4 or higher were obtained in 348 instances. *D. J. Bauer*

Papp, Karola. Tanulmány kanyaró pathomechanizmusáról. [**A Study of the Mechanism of the Pathogenesis of Measles**] *Egészségtudomány.* Budapest. 1960, v. 4, No. 1, 27–37. [36 refs.] German summary.

The author has developed an interpretation of the pathogenesis of measles which is partly hypothetical and partly based on experimental findings. It is postulated that 3 antigens are concerned. The first is the virus itself, which penetrates the body through the intact conjunctiva [see this *Bulletin*, 1959, v. 34, 969] from whence it enters the bloodstream and multiplies in the leucocytes, evoking the production of neutralizing antibody. At this stage no symptoms have yet appeared. The second antigen is water-soluble; it is not associated with the virus particle, and can be detected by skin tests. At the

beginning of the prodromal period it leaves the serum and enters the central nervous system, whence it is distributed to the skin along the peripheral nerves. Here it encounters the second antibody; this is not present in the circulation, but is postulated to arise in the capillary endothelium, and its union with the antigen causes the prodromal symptoms and the exanthem, as a result of which white cells containing virus enter the saliva and enable the infection to be transmitted by the droplet route. The third antigen is a toxin with a histamine-like effect which evokes the production of an antitoxin which can be demonstrated in the serum in the stage of convalescence. *D. J. Bauer*

PALM, C. R. & BLACK, F. L. **A Comparison of Canine Distemper and Measles Viruses.** *Proc. Soc. Exper. Biol. & Med.* 1961, July, v. 107, No. 3, 588–90, 3 figs. [12 refs.]

"Comparisons of certain physical properties of canine distemper (CDV) and measles (MV) viruses have yielded data compatible with the hypothesis that they belong to the same group. Ultrafiltration of CDV indicated a particle size between 115 and 160 mμ, a value similar to that previously reported for measles. Both viruses were inactivated by ultraviolet light at a rate of 4.5 log units per erg/cm$^2 \times 10^5$. Irradiation with 10^5 roentgens of gamma particles reduced the titer 0.4 log unit at $-70°$ and 1.0 log unit at 0°C for both CDV and MV."

HOTCHIN, J.; WEIGAND, H. **Studies of Lymphocytic Choriomeningitis in Mice. I. The Relationship between Age at Inoculation and Outcome of Infection** [HOTCHIN & WEIGAND]. *J. Immunology.* 1961, Apr., v. 86, No. 4, 392–400, 10 figs. **II. A Comparison of the Immune Status of Newborn and Adult Mice Surviving Inoculation** [WEIGAND & HOTCHIN]. *Ibid.*, 401–6, 4 figs.

I. In a continuation of previous work on the behaviour of lymphocytic choriomeningitis virus in mice [this *Bulletin*, 1959, v. 34, 690] the authors have investigated the mortality and growth rate in infant mice of 2 strains injected intracerebrally with 100 LD50 of virus at various ages up to 7 days after birth. The mortality was low in mice infected during the first 2 days of life, subsequently rising to 80–100% in mice infected on the 3rd–4th day of life. Retardation of growth was also noted.

II. In mice which had survived infection with lymphocytic choriomeningitis virus 2 hours or 1 day after birth the virus was still present in the brain in a titre of 10^6 95 days later, and the mice were immune when challenged intracerebrally after 47 and 90 days; no complement-fixing antibody could be found in the serum. The mice were therefore suffering from a persistant tolerated infection. Litters born to females with such infection up to 144 days after the original infection contained virus in high titres and were immune on challenge. The results are discussed in relation to the concept of immunological tolerance. *D. J. Bauer*

MENDELSON, C. G. & KLIGMAN, A. M. **Isolation of Wart Virus in Tissue Culture. Successful Reinoculation into Humans.** *Arch. Dermat.* 1961, Apr., v. 83, No. 4, 559–62, 4 figs.

A virus has been isolated from 2 plantar warts of myrmecia type by the inoculation of monkey kidney monolayer cultures with a combined suspension of the ground lesions. The medium was renewed every 3–5 days and a passage was made from the culture fluid every 2 weeks. Cytopathic changes appeared in the 3rd passage and became more marked during the next 3 passages; the cells showed ballooning and vacuolation with narrowing of the terminal processes, and many cells died. Culture fluid of the 6th passage was injected intradermally in the thenar eminence of 20 volunteers aged 7–20 years; typical common warts (not of myrmecia type) developed in 2 within 3 months, and in 10 volunteers within 12 months. An ultrafiltrate of a suspension of the lesions from 2 volunteers was similarly injected into 17 volunteers, 9 of whom developed typical common warts within 8 months. *D. J. Bauer*

KUWERT, E. & WINKLER, Christa. Über den Einfluss des Serumzusatzes bei der Titration des Tollwutvirus. [**The Effect of the Addition of Serum in the Titration of Rabies Virus**] *Ztschr. f.d.g. Hyg. u. ihre Grenzgebiete.* Berlin. 1961, Feb., v. 7, No. 2, 147–58, 2 figs. [24 refs.]

[An abstract of this paper appeared in the *Tropical Diseases Bulletin*, 1961, v. 58, 1343.]

IMMUNITY

ŠTERZL, J. & TRNKA, Z. Experimentální hodnocení předpokladů klonální selekční teorie tvorby protilátek. [**Experimental Evaluation of the Hypotheses of the Clonal Selection Theory of Antibody Formation**] *Československ. Epidemiol., Mikrobiol., Imunol.* Prague. 1961, v. 10, No. 3, 148–57, 2 figs. & 1 diagram. [47 refs.] English summary.

Young rabbits were injected intraperitoneally with 50×10^6 spleen cells which had previously been mixed with *Brucella suis* antigen and the course of production of specific antibody by the cells was followed over a period of 20 days. Antibody was first detected after 4–5 days; when the number of cells treated with antigen used for injection was increased 10–16 fold the latent period of antibody formation was not shortened. This finding does not support the clonal selection theory of antibody formation, which would require the latent period to be shortened on account of the more rapid formation of a clone resulting from the increase in the initial number of cells.

In further experiments cells were exposed to X-rays

in a dose of 200–300 r, which was known to inhibit the exponential multiplication of the cells. No suppression of antibody formation was noted, however. With certain exceptions (6-thioguanine, 6-mercaptopurine and aminopterin), purine and folic acid antagonists and mitotic poisons which inhibited the multiplication of the cells did not prevent them from forming antibody. These results likewise cannot be explained on the basis of the clonal selection hypothesis. *D. J. Bauer*

PEARLMAN, D. S. **Antibody Formation in Infancy.** *Amer. J. Dis. Children.* 1961, Aug., v. 102, No. 2, 239–48, 2 figs. [53 refs.]

"The ability of the infant to form antibodies has been reviewed, particularly in the light of recent investigations. Based on information indicating that the infant's ability to form antibodies is present at or soon after birth, a rationale for instituting immunizing procedures at an early age is presented."

FISHEL, C. W. & PEARLMAN, D. S. **Complement of Paired Mother-Cord Sera.** *Proc. Soc. Exper. Biol. & Med.* 1961, July, v. 107, No. 3, 695–9. [12 refs.]

"Complement hemolytic activities of sera, obtained from umbilical cords at birth, were compared to those obtained from the corresponding mothers. The lower total activity of the cord specimens was correlated with a parallel decrease in all components. Anticomplementary substances could not be detected in cord samples. The reduced concentration of complement components in cord sera was correlated with reduced levels of alpha- and beta-globulins as determined by paper electrophoresis. It may be more than coincidental that 3 of the 4 components also migrate in this region."

CHAUDHURI, A. K. MITRA, A. K. & GHOSH, B. N. **Studies on Complement. Part I: Factors Responsible in Richardson's Solution for Preservation of Complement.** *Ann. Biochem. & Exper. Med.* Calcutta. 1961, May, v. 21, No. 5, 133–8.

"Of the various reagents in Richardson's preservative solution for liquid complement, sorbitol appears to be the factor most directly responsible for the preservation of complement function since fraction C'1 of complement preserved in sorbitol-free solutions is found to deteriorate rapidly and this is the reason for the loss of lytic activity of the complement. Whether this role is played by sorbitol alone or with the help of or in conjunction with boric acid and saturated salt solution could not be definitely established in the experiments. Saturated salt solution alone preserves the complement function to some extent. Sodium azide which presumably acts as an anti-infective agent can also be replaced by 1/1000 merthiolate with equally good results.

"The above conclusions are based on a single set of experiments. Further work is in progress."

BLATTBERG, B., BANNING, P. G., MEHLER, R. E. & LEVY, M. N. **Influence of Antibiotics and Hemorrhage upon Serum Properdin Titers.** *Proc. Soc. Exper. Biol. & Med.* 1961, July, v. 107, No. 3, 620–22. [11 refs.]

SIQUEIRA, Maria & NELSON, R. A., Jr. **Platelet Agglutination by Immune Complexes and its Possible Role in Hypersensitivity.** *J. Immunology.* 1961, May, v. 86, No. 5, 516–25. [34 refs.]

The authors were concerned with observing the agglutination *in vitro* of the platelets of certain animals (guineapigs and rabbits) when placed in a mixture of small concentrations of antigen, antibody and complement, and with comparing it with the platelet agglutination characteristic of the Shwartzman reaction. The former they thought was a two-phase reaction: (1) the formation of an antigen-antibody-complement complex, and (2) the attachment of this complex to specific "receptor sites" on the surfaces of platelets to yield visible aggregates of platelets. There was no indication that antibody to the platelets was involved. Unlike investigations demonstrating independent roles for platelets and for complement in the pathogenesis of hypersensitive lesions, these results established a definitive and causal relationship between platelet agglutination and complement reacting in the presence of antigen-antibody systems. Numerous assays with washed platelets from normal human beings were consistently negative. Formation of the antigen-antibody-complement complex, but not platelet agglutination, was inhibited by citrate and heparin; ethylene-diamine tetra-acetate (EDTA) inhibited both. Agglutination of platelets occurred with fresh serum from normal rabbits and guineapigs mixed with the soluble antigens of *Salmonella typhi* and with certain dextrans reactive as "preparative" and "provocative" agents in the Shwartzman phenomenon. *D. A. Cannon*

ROSEN, F. S. **The Endotoxins of Gram-Negative Bacteria and Host Resistance.** *New England J. of Med.* 1961, May 4 & 11, v. 264, Nos. 18 & 19, 919–23; 980–85. [100 refs.]

This is an extremely interesting and well-prepared, and documented, review article which gives an overall view of current research on endotoxin as well as the clinical implications that derive from these investigations. It is obvious that in a review of this sort it is not possible to discuss detailed researches; several reviews have been published in recent years which cover very adequately particular aspects of the problem, but most general readers will find, in the opinion of the reviewer, that a study of the article will be most rewarding. The author discusses various aspects of endotoxin dealing in turn with the chemistry, physio-pathological effects, injurious results, including the Shwartzman phenomenon, the normal host defence mechanisms and protective properties.

Readers of this *Bulletin* will remember the abstract of Barry WOOD's 1958 Shattuck Lecture: "The cause of

fever" [this *Bulletin*, 1958, v. 33, 869] which was a major contribution to the study of pyrogenicity as an example of the injurious effects of endotoxin. This receives full consideration as do all the important recent contributions to the study of the fascinating effect of these complex lipopolysaccharide substances, both from the point of view of injurious agents and agents concerned with host resistance to noxious stimuli. *H. J. Bensted*

KORNFELD, Lottie & MILLER, C. P. **Disappearance Rate of Normal Bactericidins in Irradiated Mice.** *Proc. Soc. Exper. Biol. & Med.* 1961, July, v. 107, No. 3, 590–94.

PLETCITYI, D. F. Sur le rôle du système nerveux dans l'immunité (l'immunité et les types de systèmes nerveux). **[Role of the Nervous System in Immunity]** *Rev. d'Immunologie.* 1961, Apr.–June, v. 25, No. 3, 167–84, 6 figs. [17 refs.]

RAMON, G. & RICHOU, R. Les fondements de la méthode des vaccinations anatoxiques. La préparation des anatoxines. Considérations d'ordre général. **[Fundamentals of Vaccination with Toxoids, their Preparation and General Considerations]** *Rev. d'Immunologie.* 1961, Apr.–June, v. 25, No. 3, 93–121. [Refs. in footnotes.]

Miscellaneous

MANUILA, A. La crise du vocabulaire médical. Ses origines—Ses causes—Ses remèdes. **[The Origins, Causes and Remedies of the Crisis in Medical Vocabulary]** Reprinted from *Vie Méd.* 1960, Special No., 6 pp., 8 figs.

This essay is much to the point at the present time, when so much that is new—and complicated—is taking place in medicine, and therefore is impinging on medical vocabulary, and when increasing subtlety of meaning demands corresponding multiplicity of terms. On the one hand there is the dreary and awkward pedant, pointing with scorn at the unsound neologism, and on the other hand there is the ebullient coiner of jargon, who does not seem to realize that there are other languages and disciplines than his own.

Manuila takes us into history, and to the medical dictionaries of the 18th and 19th centuries—the latter described as *la belle époque des étymologistes et des puristes.* Caecostomy, for instance, is a word half latin and half Greek, and this was frowned upon by purists who preferred the homogeneous typhlostomy, but who have made no headway. Not that etymology is to be ignored; Littré, for instance, objected to *policlinique* derived from *polis*, a city, and insisted on *polyclinique* from *polus*, many; and this is accepted. [So is antibody, which dismayed Quiller-Couch one day as he sat in a doctor's waiting room and saw the word in a journal on the table there.]

But Manuila, in spite of the fact that the technical vocabulary of the doctor now amounts to 40,000 words, mostly "bastards of Greek, Latin, Graeco-Latin, Arab, English, German, Italian, Egyptian or Persian origin", recognizes the need for new terms. The important requirement is clarity, for writing is meant to be understood. He dislikes over-much synonymy, though it is not always useless, and gently suggests that the 172 synonyms for *Candida albicans* and the 21 for *Salmonella cholerae-suis* are excessive. Collective efforts have been made on a large scale to obtain international agreement on a wide range of scientific and medical terms, and on biological nomenclature, and there is, he argues, still much room for conformity between the different languages. In particular he mentions eponyms, abbreviations and symbols as obstacles to understanding.

[This is a learned and interesting essay, in beautiful language, on a subject often ignored by scientific writers. It is not an essay on writing in general, but on words and their development, a necessary and important subject.] *Charles Wilcocks*

FRANKLIN, W. & LOWELL, F. C. **Unrecognized Airway Obstruction associated with Smoking: a Probable Forerunner of Obstructive Pulmonary Emphysema.** *Ann. Intern. Med.* 1961, Mar., v. 54, No. 3, 379–86, 1 fig. [18 refs.]

Airway obstruction can be measured by recording various fractions of the forced expiratory volumes. In this study the authors have used (i) the total vital capacity (VC), (ii) the volume expired in one second "corrected" for failure to exert maximal effort at the start (FSV), (iii) the average rate of expiration between the points where 25% and 75% (E_{25-75}) and 50% and 75% have been expired (E_{50-75}).

"Expirograms" and the replies to respiratory questionnaires were obtained from about 1,000 factory workers in conjunction with routine annual or pre-employment medical examinations, including X-ray examinations of the chest. 23 subjects were eliminated because of evident cardiac or pulmonary disease. The relationship between smoking history and respiratory function was examined in 2 groups of the remainder, defined as men aged 40–60 years who were "light smokers" or "heavy smokers". The amount of smoking was calculated in "pack-years" by multiplying the daily number of packs smoked by the duration of smoking and giving cigars and pipe tobacco an arbitrary equivalent in packs of cigarettes. Light smokers were defined as having smoked less than 10 "pack-years", heavy smokers as having smoked 30 "pack-years" or more.

Comparison of the various measures of respiratory function showed in each case diminished efficiency in the 104 heavy smokers compared with the 59 light smokers. The differences in VC and FSV were not significant; the differences in E_{25-75} and E_{50-75} were. The greatest and most significant difference was shown by E_{50-75} ($P<0.01$); with this measure the mean expiratory flow was found to be 20% lower in heavy smokers than in light smokers. Elimination of pipe and cigar smokers from the heavy group increased the difference by approximately a further 10%.

The authors believe that the reduction in expiratory flow rate among smokers is the forerunner of chronic obstructive emphysema and that the data support "a causal relationship" between smoking and the disease.

Richard Doll

Book Review

ROGERS, Edward S. [M.D., M.P.H.] **Human Ecology and Health. An Introduction for Administrators.** pp. xviii+334, 28 figs. 1960. New York: The Macmillan Co. [54s.]

The author of this very interesting book states in his preface that it was not planned and written systematically, but that it evolved slowly while he was teaching graduate students in public health and discovering with them "some of the significant pieces of knowledge that lie behind an understanding of the responsibilities and widening horizons of public health and its related fields of community service". It is not a textbook but a treatise on the relationship between man and his total environment, material, spatial and cultural. It is specifically addressed, in its subtitle, to the administrator, and it attempts to lead him through a study of human ecology to an understanding of health trends and the health services evolved to meet them. Though the importance of this approach to health is being recognized increasingly there have been few books dealing with the subject. This one is, therefore, to be welcomed and not only because it fills an important vacancy, but because of its intrinsic value.

The book is divided into 4 parts. Part I devotes nearly 100 pages to the demographic background and discusses the importance of demography, theories of population growth, estimation of population, its composition and distribution and its economic and educational status. The second part, of some 20 pages, is entitled "The health status of the population of the United States". It includes sections on vital statistics and their use, and then discusses the statistical findings in two groups—those with a positive health focus (birth and life expectancy rates) and those with a negative focus (mortality and morbidity rates). It deals also with the numerous factors influencing these rates. Part III, "An ecologic approach to the concept of health and illness", in some 20 pages discusses the measurement of health status and describes the factors affecting it. There is an interesting section on positive health, and on the complexity of disease processes and, therefore, of their control.

These subjects are dealt with broadly and it is intended that they should be supplemented by lectures and discussions which would demonstrate the importance of the matters discussed. They are concerned mainly with conditions in the United States but data from other countries are quoted, and the principles underlying health problems and control at all levels of community development are discussed and illustrated. The fourth part consists of tabulated matter too bulky for the text, and of extensive quotations from numerous authoritative sources in various disciplines. The latter discuss more fully subjects referred to briefly in the text and are meant to encourage the reader to study the literature. To this end the book is excellently documented both in footnotes and in a bibliography of 11 pages which lists the sources consulted. This part also contains a number of short sections on technical methods.

This book does not cover public health systematically and it is, therefore, not sufficient as a textbook for students preparing for professional qualifications in public health. Its function is rather to educate the reader in an understanding of epidemiology and in the significance of epidemiological findings, in recognizing health problems which are evolving and the factors helping to produce them, and in studying the basic principles of public health and its relationships with other disciplines; it will set the mind exploring the philosophy of public health. This book can unhesitatingly be commended to all who are interested in the evolution of public health and who welcome the stimulus of new ideas.

T. H. Davey

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